PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 23 March 2001 (23.03.01)	
International application No. PCT/US00/20064	**Applicant's or agent's file reference** SCH-1703 WO
International filing date (day/month/year) 24 July 2000 (24.07.00)	**Priority date** (day/month/year) 22 July 1999 (22.07.99)
Applicant MULZER, Johann et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

14 February 2001 (14.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
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Form PCT/IB/331 (July 1992)

US0020064

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
SCH-1703 WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 20064	24/07/2000	22/07/1999
Applicant		
SCHERING AKTIENGESELLSCHAFT		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/20064

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/06 C07D493/04 C07D275/06 C07D417/14 C07F7/18
//(C07D493/04,313:00,303:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NICOLAU K.C. ET AL: "Total syntheses of epothilones A and B via a macro-lactonization-based strategy" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 119, no. 34, 27 August 1997 (1997-08-27), pages 7974-7991, XP002156412 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 cited in the application the whole document	1-6
X	page 7975, scheme 2, compound 19	7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 January 2001	23/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beslier, L

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 19086 A (GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH) 29 May 1997 (1997-05-29) cited in the application the whole document	1-6
X	claim 7	7
P,X	MARTIN H.J. ET AL.: "How stable are epoxides? A novel synthesis of epothilone B" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION., vol. 39, no. 3, 4 February 2000 (2000-02-04), pages 581-583, XP002156413 VERLAG CHEMIE. WEINHEIM., DE ISSN: 0570-0833 the whole document	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/20064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9719086 A	29-05-1997	DE 19542986 A	22-05-1997
		DE 19639456 A	26-03-1998
		EP 0873341 A	28-10-1998
		EP 0903348 A	24-03-1999
		JP 2000500757 T	25-01-2000

  J. Am. Chem. Soc. **1997**, *119*, 7974−7991

Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy

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Received April 7, 1997[⊗]

Abstract: The total syntheses of epothilones A (**1**) and B (**2**) and several analogues thereof are described. The reported strategy relies on a macrolactonization approach and features selective epoxidation of the macrocycle double bond in precursors **3** and **4** (Scheme 1), respectively, as well as high convergency and flexibility. Building blocks **9**−**12** and **15** were constructed by asymmetric processes and coupled via Wittig, aldol, and macrolactonization reactions to afford the basic skeleton of epothilones and that of several of their analogues by a relatively short route. The utilization of intermediate **14**, obtained via a stereoselective Wittig reaction and its Enders coupling to SAMP hydrazone **13** (Scheme 8), in combination with a stereoselective aldol reaction with the modified substrate **69** (Scheme 10) improved the stereoselectivity and efficiency of the total synthesis of these new and highly potent microtubule binding antitumor agents.

1. Introduction

Epothilones A (**1**) and B (**2**) are two architecturally novel natural products recently isolated from the myxobacteria *Sorangium cellulosum* strain 90[1,2] and possess impressive microtubule binding affinities and antitumor properties.[1−4] Their molecular structures have been secured by a combination of spectroscopic and X-ray crystallographic techniques.[1,2] Interestingly, and despite their structural difference from Taxol, the epothilones were found to bind to the same region on microtubules[4] and to displace Taxol from its binding site.[5,6] The higher potency of these new compounds, and their effectiveness against certain drug-resistant tumor cell lines,[3,4] generated a great deal of excitement among chemists,[7] biologists, and clinicians. At least five total syntheses[8−11] of epothilone A (**1**) have already been achieved. The two from these laboratories were based on an olefin metathesis approach[9] and a macrolactonization approach.[10] The total synthesis of epothilone B (**2**) and its analogues has also been reported first by Danishefsky[12] and then by us[13] in preliminary communications. Here, we report the details of the total synthesis of both epothilones A (**1**) and B (**2**) and of a number of analogues of these compounds by our macrolactonization strategy.[10]

2. Retrosynthetic Analysis

Scheme 1 outlines the macrolactonization-based retrosynthetic analysis of epothilones A (**1**) and B (**2**). Thus, retrosynthetic removal of the epoxide oxygen from **1** and **2** reveals the corresponding *Z*-olefins, **3** and **4**, as potential precursors, respectively. The second major retrosynthetic step along this route is the disconnection of the macrocyclic ring at the lactone site, leading to hydroxy acids **5** and **6** as possible key intermediates. Moving further along the retrosynthetic path, an aldol-type disconnection allows the generation of keto acid **9** as a common intermediate and aldehydes **7** and **8** as reasonable building blocks for **5** and **6**, respectively. Keto acid **9** can be envisioned to arise from an asymmetric allylboration[14] of the corresponding aldehyde, followed by appropriate elaboration of the terminal olefin. The larger intermediates, **7** and **8**, can be disconnected by two slightly different ways. The first

⊗ Abstract published in *Advance ACS Abstracts,* August 1, 1997.

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(2) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1567−1569.

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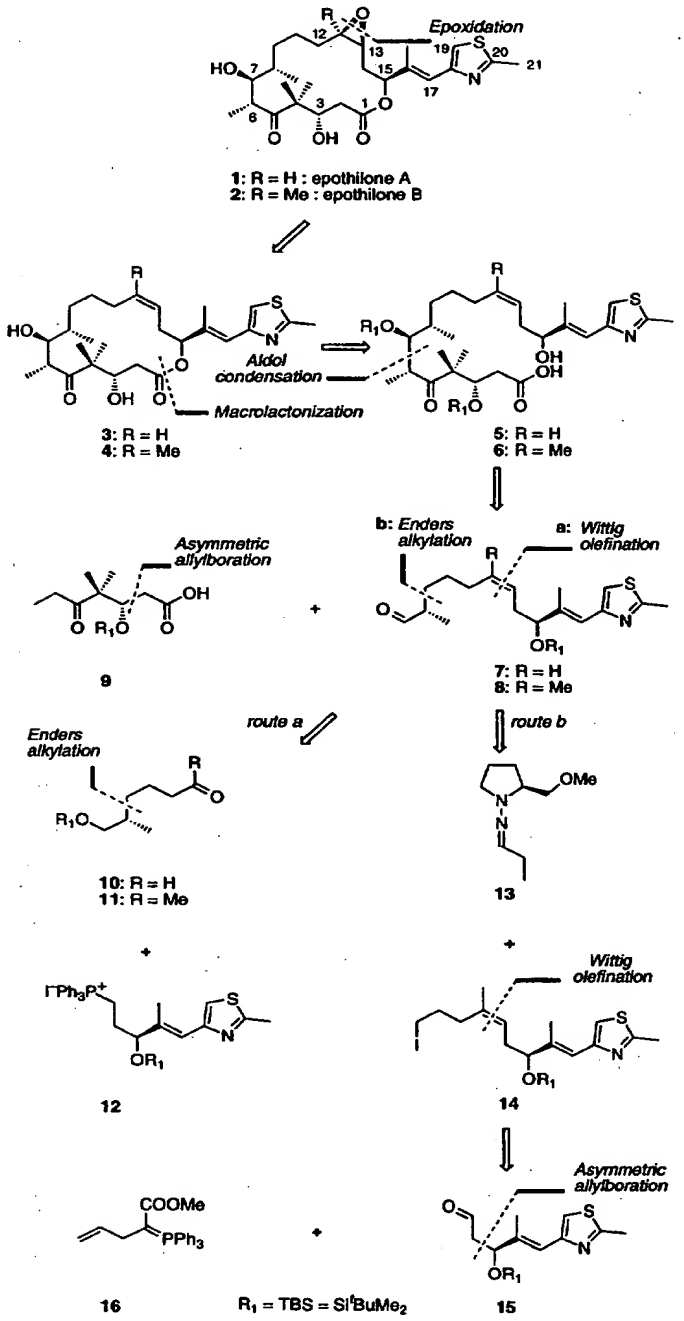
S0002-7863(97)01110-4 CCC: $14.00

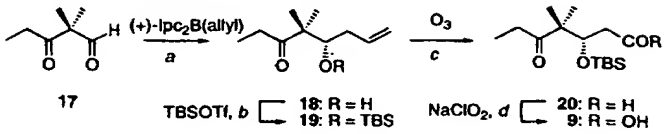
Scheme 1. Molecular Structures and Retrosynthetic Analysis of Epothilones A (1) and B (2)



disconnection (route a) involves a retro-Wittig type reaction accompanied by a number of functional group interchanges, leading to compounds **10**–**12**. The second disconnection, specifically sought for its potential to address the geometry issue of the trisubstituted double bond of epothilone B (**2**) (route b), involves (i) a retro-Enders alkylation,[15] leading to hydrazone **13** and iodide **14**, and (ii) a retro-Wittig type disconnection of the latter intermediate (**14**) to reveal aldehyde **15** and stabilized ylide **16** as potential building segments. An asymmetric allylboration of **15** then points to Brown's chiral allylborane[14] and an aldehyde carrying the required thiazole moiety as potential starting points.

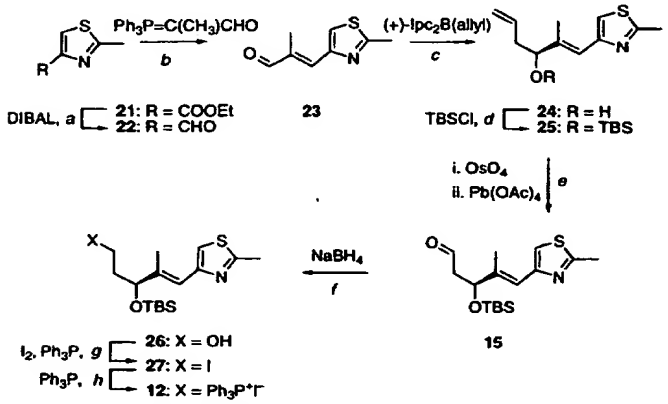
(15) (a) Enders, D. *Asymmetric Synth.* **1984**, *3*, 275–339. (b) Enders, D.; Klatt, M. *Synthesis* **1996**, 1403–1418.

Scheme 2. Synthesis of Keto Acid **9**[a]



[a] Reagents and conditions: (a) 1.2 equiv of (+)-Ipc_2B(allyl), Et_2O, −100 °C, 0.5 h, 74% (ee >98% by Mosher ester analysis); (b) 1.1 equiv of TBSOTf, 1.2 equiv of 2,6 lutidine, CH_2Cl_2, 25 °C, 98%; (c) O_3, CH_2Cl_2, −78 °C, 0.5 h; then 1.2 equiv Ph_3P, −78 → 25 °C, 1 h, 90%; (d) 3.0 equiv of $NaClO_2$, 4.0 equiv of 2-methyl-2-butene, 1.5 equiv of NaH_2PO_4, ^tBuOH:H_2O (5:1), 25 °C, 2 h, 93%.

Scheme 3. Synthesis of Phosphonium Salt **12** and Aldehyde **15**[a]



[a] Reagents and conditions: (a) 1.6 equiv of DIBAL, CH_2Cl_2, −78 °C, 2 h, 90%; (b) $Ph_3P{=}C(CH_3)CHO$, benzene, reflux, 98%; (c) 1.5 equiv of (+)-Ipc_2B(allyl), Et_2O, −100 °C, 0.5 h, 96% (ee >97% by Mosher ester analysis); (d) 1.2 equiv TBSCl, 1.5 equiv of imidazole, DMF, 0 → 25 °C, 2 h, 99%; (e) i. 1.0 mol % OsO_4, 1.1 equiv of 4-methylmorpholine *N*-oxide (NMO), THF:^tBuOH:H_2O (1:1:0.1), 0 → 25 °C, 12 h, 95%; ii. 1.3 equiv of $Pb(OAc)_4$, EtOAc, 0 °C, 0.5 h, 98%, (f) 2.5 equiv of $NaBH_4$, MeOH, 0 °C, 15 min, 96%; (g) 1.5 equiv of I_2, 3.0 equiv of imidazole, 1.5 equiv of Ph_3P, Et_2O:MeCN (3:1), 0 °C, 0.5 h, 89%; (h) 1.1 equiv Ph_3P, neat, 100 °C, 2 h, 98%.

3. Total Synthesis

a. Construction of Building Blocks. The strategy derived from the retrosynthetic analysis discussed above (Scheme 1) required building blocks **9**–**12**, **15**, and related compounds. Their construction in optically active form proceeded as follows. Scheme 2 summarizes the synthesis of keto acid **9** starting with the known keto aldehyde **17**.[16] Thus, addition of (+)-Ipc_2B-(allyl)[14] to **17** in ether at −100 °C resulted in the formation of enantiomerically enriched alcohol **18** (74% yield, ee > 98% by Mosher ester determination).[17] Silylation of **18** with *tert*-butyldimethylsilyl triflate (TBSOTf) furnished, in 98% yield, silyl ether **19**. The conversion of terminal olefin **19** to carboxylic acid **9** was carried out in two steps: (i) ozonolysis in CH_2Cl_2 at −78 °C followed by exposure to Ph_3P to give aldehyde **20** (90% yield) and (ii) oxidation of **20** with $NaClO_2$ in the presence of 2-methyl-2-butene and NaH_2PO_4 in ^tBuOH–H_2O (5:1) (93% yield).

The synthesis of the thiazole-containing fragments **15** and **12** was accomplished as shown in Scheme 3. Thus, the known thiazole derivative **21**[18] was reduced with DIBAL (1.6 equiv, CH_2Cl_2, −78 °C) to aldehyde **22** (90% yield), which reacted

(16) Inuka, T.; Yoshizawa, R. *J. Org. Chem.* **1967**, *32*, 404–407.

(17) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519. (b) Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, H. *Tetrahedron Lett.* **1988**, *29*, 4731–4734. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

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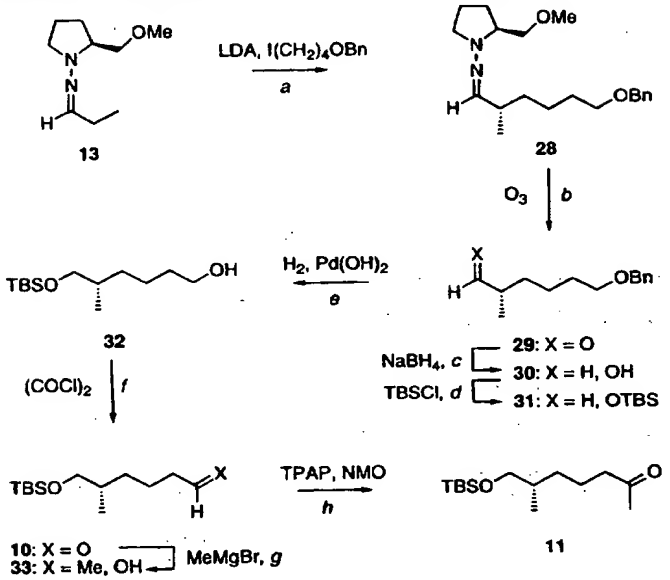
Scheme 4 Synthesis of Aldehyde **10** and Ketone **11**[a]



[a] Reagents and conditions: (a) 1.1 equiv of LDA, THF, 0 °C, 8 h; then 1.5 equiv of 4-iodo-1-(benzyloxy)butane in THF, at −100 → 0 °C, 6 h, 92% (de > 98% by ^{1}H NMR); (b) O_3, CH_2Cl_2, −78 °C, 77% or MeI, 60 °C, 5 h; then 3 N aqueous HCl, *n*-pentane, 25 °C, 1 h, 86%; (c) 3.0 equiv of $NaBH_4$, MeOH, 0 °C, 15 min, 98%; (d) 1.5 equiv of TBSCl, 2.0 equiv of Et_3N, CH_2Cl_2, 0 → 25 °C, 12 h, 95%; (e) H_2, $Pd(OH)_2$ cat., THF, 50 psi, 25 °C, 15 min, 95%; (f) 2.0 equiv of $(COCl)_2$, 4.0 equiv of DMSO, 6.0 equiv of Et_3N, CH_2Cl_2, −78 → 0 °C, 1.5 h, 98%; (g) 1.5 equiv of MeMgBr, THF, 0 °C, 15 min, 84%; (h) 1.5 equiv of NMO, 0.05 equiv of tetrapropylammonium perruthenate (TPAP), 4 Å MS, CH_2Cl_2, 25 °C, 45 min, 96%.

with the appropriate stabilized ylide [Ph_3P=C(Me)CHO] in benzene at 80 °C to afford the required (*E*)-α,β-unsaturated-aldehyde **23**[7a,b,h,9] in 98% yield. Addition of (+)-Ipc_2B(allyl)[14] to **23** in ether/pentane at −100 °C gave allylic alcohol **24** in 96% yield (>97% ee by Mosher ester analysis).[17] Protection of the hydroxyl group in **24** as a TBS ether (TBSCl, imidazole, DMF, 99% yield), followed by chemoselective dihydroxylation (OsO_4 cat., NMO)[19] of the terminal olefin (95% yield) and Pb(OAc)$_4$ cleavage of the resulting diol (98% yield), furnished aldehyde **15** via intermediate **25**. Finally, $NaBH_4$ reduction of **15** (96% yield), followed by iodination (I_2, imidazole, Ph_3P, 89% yield) and phosphonium salt formation (Ph_3P, neat, 100 °C, 98% yield) gave the requisite fragment **12** via the intermediacy of alcohol **26** and iodide **27**.

The construction of aldehyde **10** and ketone **11** proceeded from SAMP hydrazone **13** as shown in Scheme 4. Thus, reaction of propionaldehyde with SAMP[20] furnished **13**, which upon sequential treatment with LDA (THF, 0 °C) and 4-iodo-1-(benzyloxy)butane (THF, −100 → 0 °C) led to compound **28** in 92% yield and >98% de (^{1}H NMR). Cleavage of the hydrazone moiety by exposure to ozone (CH_2Cl_2, −78 °C, 77% yield) or by treatment with MeI at 60 °C followed by acidic workup (aqueous HCl, 86% yield),[21] followed by $NaBH_4$ reduction of the resulting aldehyde (**29**), furnished alcohol **30** in 98% yield. The latter compound (**30**) was then silylated with TBSCl in CH_2Cl_2 in the presence of Et_3N and 4-DMAP to afford silyl ether **31** in 95% yield. Cleavage of the benzyl ether in **31** by hydrogenolysis [H_2, $Pd(OH)_2$ cat., THF, 50 psi] gave primary alcohol **32** (95% yield), which was smoothly oxidized to the desired aldehyde **10** under Swern conditions[22] [$(COCl)_2$, DMSO, Et_3N, 98% yield]. Addition of MeMgBr to **10** proceeded in 84% yield and was followed by TPAP–NMO oxidation[23] of the resulting secondary alcohol (**33**) to give the other required building block, ketone **11**, in 96% yield.

With the appropriate building blocks at hand, the convergent approach to epothilones A (**1**) and B (**2**) could now enter its second phase.

b. Total Synthesis of Epothilone A. The couplings of building blocks **9**, **10**, and **12** and the total synthesis of epothilone A (**1**) and its 6*S*,7*R*-diastereoisomers (**44** and **45**) are shown in Scheme 5. Thus, generation of the ylide from phosphonium salt **12** with sodium bis(trimethylsilyl)amide (NaHMDS), followed by reaction with aldehyde **10** resulted in the formation of the desired *Z*-olefin **34** ($J_{12,13}$ = 10.8 Hz, obtained from decoupling experiments) as the predominant product in 77% yield [*Z*:*E* ca. 9:1; the minor isomer (*E*) was removed chromatographically in subsequent steps]. Parenthetically, key intermediate **34** was also prepared by Wittig coupling of phosphonium salt **47** and aldehyde **15** in a reversal of the reacting functionalities of the two fragments as shown in Scheme 6. Thus, alcohol **32** was directly converted to iodide **46** by the action of I_2, imidazole, and Ph_3P (91% yield) and then to phosphonium salt **47** by heating with Ph_3P (91% yield). Generation of the ylide from **47** with equimolar amounts of NaHMDS in THF, followed by reaction with aldehyde **15** yielded *Z*-olefin **34** in 69% and in ca. 9:1 ratio with its *E*-isomer.

Returning to Scheme 5, selective desilylation of the primary hydroxyl group from **34** was achieved by the action of camphorsulfonic acid (CSA) in MeOH:CH_2Cl_2 (1:1),[24] leading to hydroxy compound **35** in 86% yield. Oxidation of **35** to aldehyde **7** was then carried out using SO_3·pyr., DMSO, and Et_3N (94% yield).[25] With the availability of **7**, we were then in a position to investigate its aldol condensation with keto acid **9**. It was found that the optimum conditions for this coupling reaction required generation of the dilithio derivative of **9** (1.2 equiv) with 3.0 equiv of lithium diisopropylamide (LDA) in THF (−78 → −40 °C), followed by addition of aldehyde **7** (1.0 equiv), resulting in the formation of a mixture of the desired product **36a** and its 6*S*,7*R*-diastereoisomer **36b** in ca. 1:1 ratio and in high yield. Despite the lack of stereoselectivity in this reaction, the result was welcome at least with regard to the prospect it provided for the construction of the 6*S*,7*R*-diastereoisomer of epothilones A and B. This mixture was then carried through to the stage of carboxylic acids **38** and **39** (Scheme 5), where it was chromatographically separated to its components. Thus, exposure of **36a,b** to excess of TBSOTf and 2,6-lutidine furnished a mixture of tetra-silylated products **37a,b**, which was then briefly treated with K_2CO_3 in MeOH[26] to afford, after silica gel flash or preparative layer chromatography, carboxylic acids **38** (31% overall yield from **7**) and **39** (30% overall yield from **7**) (**38**: R_f = 0.61; **39**: R_f = 0.70, silica gel, 5% MeOH in CH_2Cl_2). The indicated stereochemistry at C7 and C6 in compounds **38** and **39** was assigned later and was based on the successful conversion of **38** to epothilone A (**1**) as described below.

(19) (a) Schneider, W. P.; McIntosh, A. V. U.S. Patent 2,769,824, November 6, 1956. (b) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976. (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(20) (a) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933–2960. (b) Enders, D.; Tiebes, J.; De Kimpe, N.; Keppens, M.; Stevens, C.; Smagghe, G.; Betz, O. *J. Org. Chem.* **1993**, *58*, 4881–4884. (c) Enders, D.; Plant, A.; Backhaus, D.; Reinhold, U. *Tetrahedron* **1995**, *51*, 10699–10714. We thank Prof. Enders for a generous gift of SAMP.

(21) Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bergbreiter, D. E. *J. Am. Chem. Soc.* **1979**, *101*, 5654–5659.

(22) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43* 2480–2482.

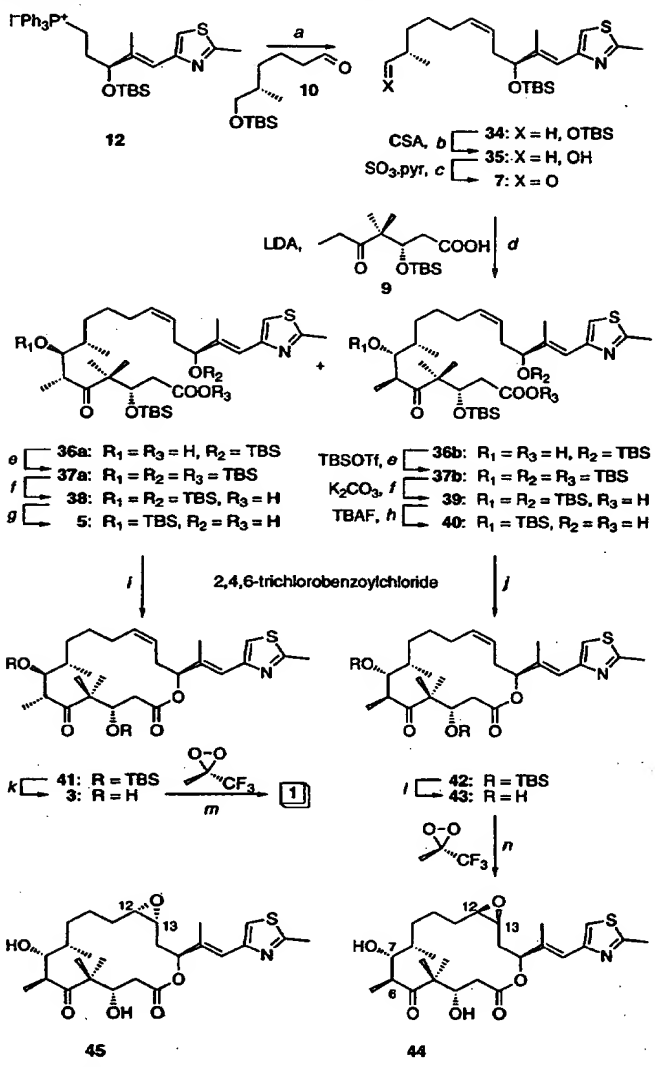
(23) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13–19.

(24) Nelson, T. D; Crouch, R. D. *Synthesis* **1996**, 1031–1069.

(25) Parikh, J. R.; von Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

(26) Morton, D. R.; Thompson, J. L. *J. Org. Chem.* **1978**, *43*, 2102-2106.

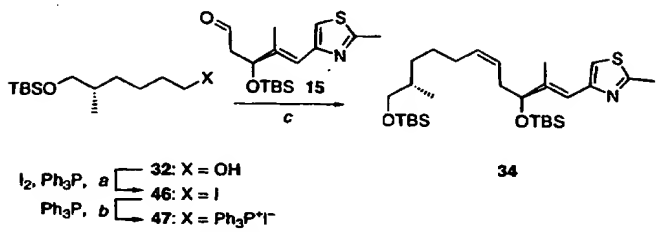
Scheme 5. Total Synthesis of Epothilone A (**1**) and Its 6*S*,7*R*-Diastereoisomers (**44** and **45**)[a]



[a] Reagents and conditions: (a) 1.2 equiv of **12**, 1.2 equiv of NaHMDS, THF, 0 °C, 15 min, then add 1.0 equiv of aldehyde **10**, 0 °C, 15 min, 77% (*Z*:*E* ca. 9:1); (b) 1.0 equiv of CSA portionwise over 1 h, CH_2Cl_2:MeOH (1:1), 0 → 25 °C, 0.5 h, 86%; (c) 2.0 equiv of SO_3·pyr., 10.0 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, 25 °C, 0.5 h, 94%; (d) 3.0 equiv of LDA, THF, 0 °C, 15 min; then 1.2 equiv of **9** in THF, −78 → −40 °C, 0.5 h; then 1.0 equiv of **7** in THF at −78 °C, high yield of **36a** and its 6*S*,7*R*-diastereoisomer **36b** (ca. 1:1 ratio); (e) 3.0 equiv of TBSOTf, 5.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h; (f) 2.0 equiv of K_2CO_3, MeOH, 25 °C, 15 min, 31% of **38** and 30% of 6*S*,7*R*-diastereoisomer **39** from **7**; (g) 6.0 equiv of TBAF, THF, 25 °C, 8 h, 78%; (h) same as g, 82%; (i) 5.0 equiv of 2,4,6-trichlorobenzoyl-chloride, 6.0 equiv of Et_3N, THF, 25 °C, 15 min; then add to a solution of 10.0 equiv of 4-DMAP in toluene (0.002 M based on **5**), 25 °C, 0.5 h, 90%; (j) same as i, 85%; (k) 20% CF_3COOH (by volume) in CH_2Cl_2, 0 °C, 1 h, 92%; (l) same as k, 95%; (m) methyl(trifluoromethyl)dioxirane, MeCN, 0 °C, 75% (ca. 5:1 ratio of diastereoisomers), see ref 27); (n) same as m, 87% (**44**:**45** ca. 2:1 ratio of diastereoisomers, tentative stereochemistry).

At this stage, it was necessary to selectively remove the TBS group from the allylic hydroxyl group of **38**, so as to allow macrolactonization of the *seco*-acid substrate (**5**). This goal was achieved by treatment of **38** with tetra-*n*-butylammonium fluoride (TBAF) in THF at 25 °C, generating the desired hydroxy acid **5** in 78% yield. The key macrolactonization reaction of **5** was carried out using the Yamaguchi method[27] (2,4,6-trichlorobenzoyl chloride, Et_3N, 4-DMAP) at 25 °C, affording compound **41** in 90% yield. Removal of both TBS groups from **41** (CF_3COOH, CH_2Cl_2, 0 °C) furnished diol **3** in 92% yield. Finally, treatment of **3** with methyl(trifluoromethyl)-dioxirane[28] led cleanly to epothilone A (**1**) (62% yield) and its α-epoxide epimer (13% yield). The reaction of macrocyclic olefin **3** with *m*CPBA gave a number of other products as described in detailed in the preceding article.[29] Synthetic epothilone A (**1**) was chromatographically purified (preparative thin-layer chromatography, silica gel) and exhibited properties identical to those of an authentic sample (TLC, HPLC, $[\alpha]_D$, IR, ^1H and ^{13}C NMR, and HRMS).[30]

Scheme 6. Synthesis of Compound **34**[a]



[a] Reagents and conditions: (a) 1.5 equiv of I_2, 3.0 equiv of imidazole, 1.5 equiv of Ph_3P, Et_2O:MeCN (3:1), 0 °C, 0.5 h, 91%; (b) 1.1 equiv of Ph_3P, neat, 100 °C, 2 h, 91%; (c) 1.2 equiv of **47**, 1.2 equiv of NaHMDS, THF, 0 °C, 15 min; then add 1.0 equiv of aldehyde **15**, 0 °C, 15 min, 69% (*Z*:*E* ca. 9:1).

A similar sequence was followed for the synthesis of the 6*S*,7*R*-diastereoisomers **44** and **45** of epothilone A (**1**) from compound **39** (Scheme 5) via intermediates **40** (82% yield from **39**), **42** (85% yield from **40**), and **43** (95% yield from **42**). Epothilone **44** was obtained as the major product, together with its α-epoxide epimer **45** (87% total yield, ca. 2:1 ratio), from olefinic precursor **43** by methyl(trifluoromethyl)dioxirane epoxidation.[28] The epoxide stereochemistry assignments in **44** and **45** are tentative.

c. Total Synthesis of Epothilone B. The first approach to epothilone B (**2**) was designed with the aim of delivering not only the natural substance but also its 12*S*-diastereoisomer **58** (Scheme 7), which in turn required the generation of both 12*Z*- and 12*E*-olefins. To this end, the ylide generated from phosphonium salt **12** with equimolar amounts of NaHMDS in THF was reacted with ketone **11** to afford a mixture of *Z*- and *E*-olefins **48** (ca. 1:1 ratio) in 73% total yield. This mixture was carried through the sequence to the stage of carboxylic acids **52′** and **53′** (see Scheme 7 for details), which were chromatographically separable. Carboxylic acid **53′** (mixture of geometrical isomers) with the wrong stereochemistry at C6 and C7 (6*S*,7*R*) was abandoned at this stage, whereas the mixture of *Z*- and *E*-isomers **52′** with the correct stereochemistry at C6 and C7 (6*R*,7*S*) was taken to the macrolactone stage (compounds **54** and **55**) via hydroxy acid **6′**, by (i) selective desilylation of the C15 hydroxyl group (TBAF, THF, 75% yield) and (ii) Yamaguchi cyclization (37% yield of **54**, plus 40% of **55**).[27] Deprotection of bis(silyl ether) **54** by treatment with CF_3COOH in CH_2Cl_2 afforded diol **4** in 91% yield. Finally, epoxidation of **4** with *m*CPBA in benzene at 3 °C gave epothilone B (**2**) together with its α-epoxide epimer **57** in 66% total yield and

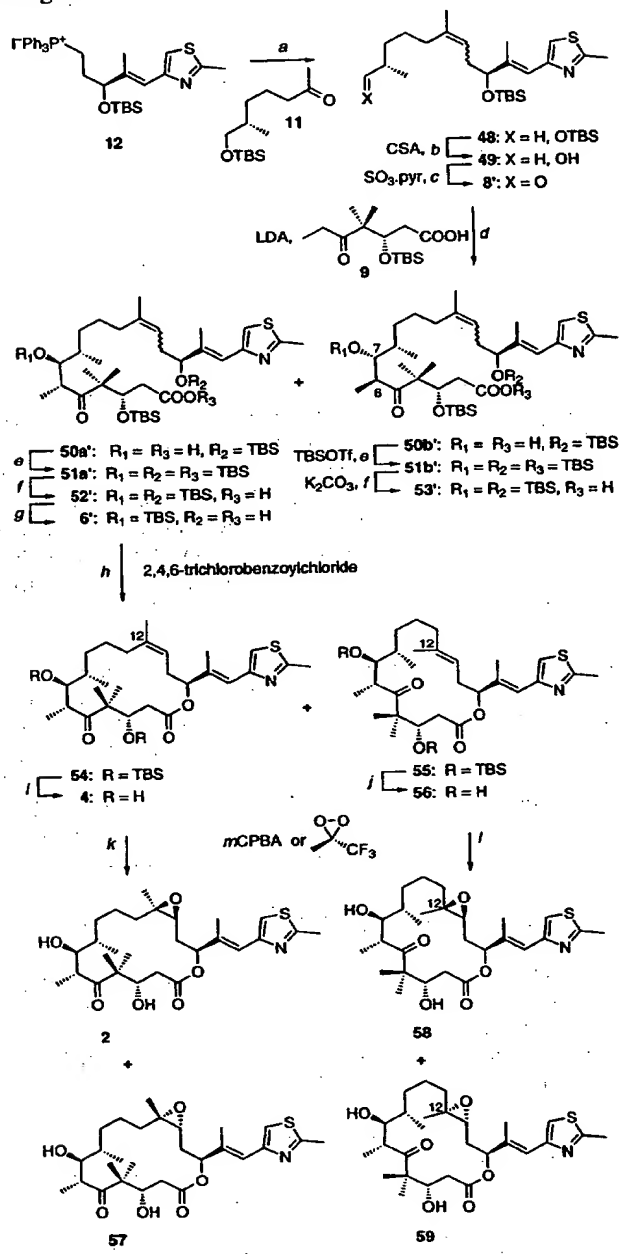
(27) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Mulzer, J.; Mareski, P. A.; Buschmann, J.; Luger, P. *Synthesis* **1992**, 215−228. (c) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem. Eur. J.* **1996**, *2*, 847−868.

(28) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887−3889.

(29) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960−7973 (preceding paper).

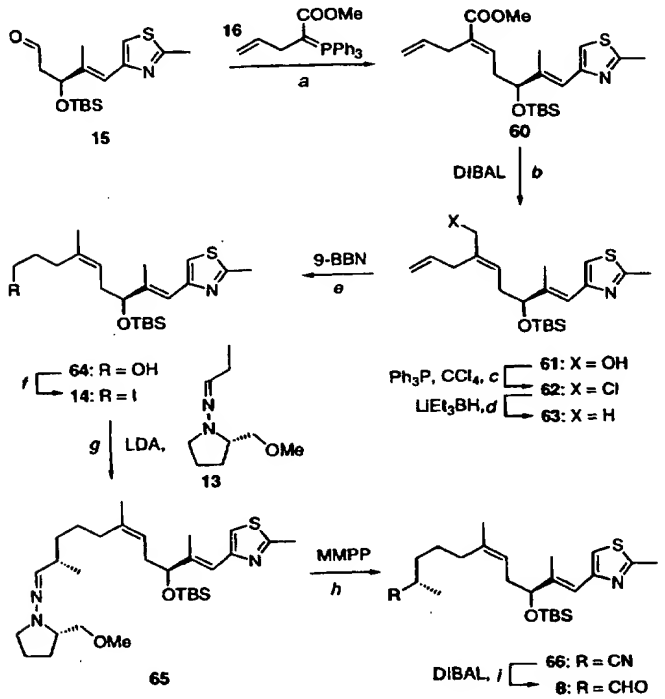
(30) We thank Dr. G. Höfle for samples of natural epothilones A (**1**) and B (**2**).

Scheme 7. Total Synthesis of Epothilone B (2) and Analogues[a]



[a] Reagents and conditions: (a) 1.5 equiv of **12**, 1.5 equiv of NaHMDS, THF, 0 °C, 15 min, then add 1.0 equiv of ketone **11**, −20 °C, 12 h, 73% (*Z*:*E* ca. 1:1); (b) 1.0 equiv of CSA portionwise over 1 h, CH_2Cl_2:MeOH (1:1), 0 °C; then 25 °C, 0.5 h, 97%; (c) 2.0 equiv of SO_3·pyr., 10.0 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, 25 °C, 0.5 h, 95%; (d) 3.0 equiv of LDA, THF, 0 °C, 15 min; then 1.2 equiv of **9** in THF, −78 → −40 °C, 0.5 h; then 1.0 equiv of **8'** in THF at −78 °C, high yield of **50a'** and its 6*S*,7*R*-diastereoisomer **50b'** (ca. 1:1 ratio); (e) 3.0 equiv of TBSOTf, 5.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h; (f) 2.0 equiv of K_2CO_3, MeOH, 25 °C, 15 min, 31% of **52'** and 30% of 6*S*,7*R*-diastereoisomer **53'** from **8'**; (g) 6.0 equiv of TBAF, THF, 25 °C, 8 h, 75%; (h) 1.3 equiv of 2,4,6-trichlorobenzoylchloride, 2.2 equiv of Et_3N, THF, 0 °C, 1 h; then add to a solution of 10.0 equiv of 4-DMAP in toluene (0.002 M based on **6'**), 25 °C, 12 h, 37% of **54**; and 40% of **55**; (i) 20% CF_3COOH (by volume) in CH_2Cl_2 −10 → 0 °C, 1 h, 91%; (j) same as i, 89%; (k) dimethyldioxirane, CH_2Cl_2, −50 °C, 75% (**2**:**57** ca. 5:1 ratio of diastereoisomers) or 1.5 equiv of *m*CPBA, benzene, 3 °C, 2 h, 66% (**2**:**57** ca. 5:1 ratio of diastereoisomers) or methyltrifluoromethyl)dioxirane, MeCN, 0 °C, 85% (**2**:**57** ca. 5:1 ratio of diastereoisomers); (l) 1.5 equiv of *m*CPBA, benzene, 3 °C, 2 h, 73% (**58**:**59** ca. 1:4 ratio of stereoisomers) or methyl(trifluoromethyl)dioxirane, MeCN, 0 °C, 86% (**58**:**59** ca. 1:1 ratio of diastereoisomers).

Scheme 8. Stereoselective Synthesis of Aldehyde **8** for Epothilone B (**2**)[a]



[a] Reagents and conditions: (a) 1.5 equiv of **16**, benzene, reflux 5 h, 95%; (b) 3.0 equiv of DIBAL, THF, −78 °C, 2 h, 98%; (c) 2.0 equiv of Ph_3P, CCl_4, reflux, 24 h, 83%. (d) 2.0 equiv of $LiEt_3BH$, THF, 0 °C, 1 h, 99%; (e) 1.2 equiv of 9-BBN, THF, 0 °C, 2 h, 91%; (f) 1.5 equiv of I_2, 3.0 equiv of imidazole, 1.5 equiv of Ph_3P, Et_2O:MeCN (3:1) 0 °C, 0.5 h, 92%; (g) 1.5 equiv of **13**, 1.5 equiv of LDA, THF, 0 °C, 8 h; then 1.0 equiv of **14** in THF, −100 → −20 °C, 10 h, 70%; (h) 2.5 equiv of monoperoxyphthalic acid, magnesium salt (MMPP), MeOH:phosphate buffer pH7 (1:1), 0 °C, 1 h, 80%; (i) 2.0 equiv of DIBAL, toluene, −78 °C, 1 h, 82%.

ca. 5:1 ratio (^1H NMR), while the use of dimethyldioxirane,[31] first reported by Danishefsky,[8a,12] gave **2** and **27** in 75% total yield in the same ratio (ca. 5:1 in favor of **2**). Epoxidation of **4** with methyl(trifluoromethyl)dioxirane[28] in CH_3CN at 0 °C improved the yield of epothilone B (**2**) and its α-epimer **57** to 85% but did not significantly change the diastereoselectivity of the reaction. Epothilone B (**2**) was purified by silica gel preparative layer chromatography and exhibited identical properties (TLC, HPLC, $[\alpha]_D$, IR, ^1H and ^{13}C NMR, and HRMS) with those of an authentic sample.[30]

By the same sequence, and in similar yields, the macrocycle **55** containing the *E*-endocyclic double bond (Scheme 7) was converted to the 12*S*-epimeric epothilone B **58** and its α-epoxy epimer **59** via dihydroxy macrocyclic compound **56** [epoxidation with methyl(trifluoromethyl)dioxirane].[28] The stereochemistry of epoxides **58** and **59** was tentatively assigned by comparisons with the corresponding epothilone A epoxides whose stereochemistry was determined by NMR spectroscopy and molecular dynamics computations and molecular modeling as described in the preceding article[29] (see also Supporting Information for $^1H-^1H$ NOESY and $^1H-^1H$ COSY).

To improve the efficiency of the route to epothilone B (**2**), a more stereoselective total synthesis was devised and executed as follows. Scheme 8 addresses the stereoselective construction of intermediate **8** with the 12*Z*-geometry. Thus, condensation of the stabilized ylide **16** [obtained from 4-bromo-1-butene by (i) phosphonium salt formation, (ii) anion formation with

(31) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847−2853.

NaHMDS, and (iii) quenching with MeOC(O)Cl][32] with aldehyde **15** proceeded smoothly to afford olefinic compound **60** in 95% yield and as a single isomer. Reduction of the methyl ester in **60** with DIBAL resulted in the formation of allylic alcohol **61** (98% yield), which was deoxygenated by first reacting it with Ph_3P-CCl_4 and then with $LiEt_3BH$,[33] to afford the desired trisubstituted 12*Z*-olefin **63**, via chloride **62**, in 82% overall yield. The latter compound **63** was regioselectively hydroborated with 9-BBN and converted to the primary alcohol **64** (91%), which was then treated with I_2–imidazole–Ph_3P to afford iodide **14** (92% yield). This iodide was then used in an Enders alkylation reaction with SAMP hydrazone **13** to give compound **65** as a single isomer (^1H NMR) and in 70% yield. Treatment of hydrazone **65** with monoperoxyphthalic acid magnesium salt (MMPP) in MeOH:phosphate pH 7 buffer (1:1)[20c,34] resulted in clean conversion to nitrile **66** (80% yield), which formed aldehyde **8** (82% yield) upon exposure to DIBAL at −78 °C in toluene solution.

The homogeneous aldehyde **8** was converted to epothilone B (**2**) by the sequence depicted in Scheme 9. Thus, condensation of the dianion of **9** with **8** as before (Scheme 7), produced two diastereoisomers, **50a** (6*R*,7*S* stereoisomer) and **50b** (6*S*,7*R* stereoisomer), in high yield and in ca. 1.3:1.0 ratio (**50a**:**50b**). This mixture was carried through the indicated sequence to carboxylic acids **52** (32% overall yield from **8**) and **53** (28% overall yield from **8**), which were separated by silica gel preparative layer or flash column chromatography and taken individually further along the sequence as described for the corresponding stereoisomeric mixtures shown in Scheme 7. Thus, **52** was selectively deprotected with TBAF to afford hydroxy acid **6** (73% yield), which was then cyclized to macrolactone **54** in 77% yield by the Yamaguchi method.[27] The conversion of **54** to epothilone B (**2**) and its α-epoxide epimer **57** has already been described above (Scheme 7).

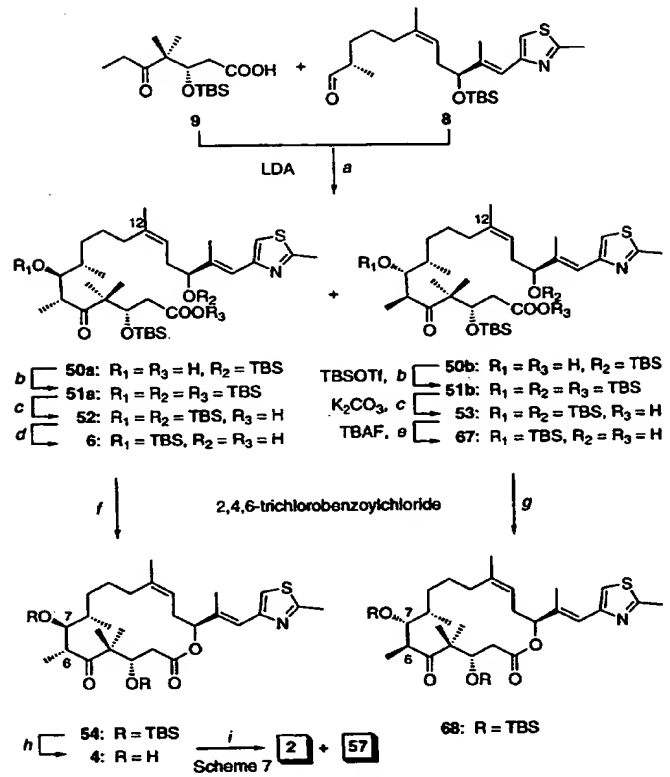
In an effort to improve the diastereoselectivity of the aldol condensation between C1–C6 and C7–C15 fragments, the following chemistry was explored (Scheme 10). Thus, ketone **69** [prepared from ketone **20** (Scheme 2) by selective reduction, followed by silylation] was converted to its enolate with stoichiometric amounts of LDA and reacted with aldehyde **8** (*Z*-isomer), affording coupling products **70** and **71** in 85% total yield and ca. 3:1 ratio, with the desired compound **70** predominating as proven by its conversion to **52** and epothilone B (**2**). Thus, chromatographic purification (silica gel, 20% ether in hexanes) led to **70**, which was efficiently transformed to the previously synthesized intermediate **52** (Scheme 9) as follows. The newly generated hydroxyl group in **70** was silylated with TBSOTf-2,6-lutidine to furnish **72** (96% yield), which was then selectively desilylated at the primary position by the mild action of camphorsulfonic acid (CSA) in $MeOH-CH_2Cl_2$, leading to **73** (85%). Finally, sequential oxidation of the primary alcohol with $(COCl)_2$–DMSO–Et_3N (95% yield) and $NaClO_2-NaH_2PO_4$ (90% yield) led to hydroxy acid **52** via aldehyde **74**. The conversion of **52** to **2** has already been described above (Scheme 9). This sequence represents a stereoselective and highly efficient synthesis of epothilone B (**2**) and opens the way for the construction of further analogues within this important family of microtubule binding agents.

(32) (a) Marshall, J. A.; DeHoff, B. S.; Cleary, D. G. *J. Org. Chem.* **1986**, *51*, 1735–1741. (b) Bestmann, H. J. *Angew. Chem., Int. Ed. Engl.* **1965**, 645–660.

(33) Heissler, D.; Jenn, T.; Nagano, H. *Tetrahedron Lett.* **1991**, *32*, 7587–7590.

(34) Enders, D.; Backhaus, D.; Runsink, J. *Tetrahedron* **1996**, *52*, 1503–1528.

Scheme 9. First Stereoselective Total Synthesis of Epothilone B (**2**)[a]



[a] Reagents and conditions: (a) 3.0 equiv of LDA, THF, 0 °C, 15 min; then 1.2 equiv of **9** in THF, −78 → −40 °C, 0.5 h, then 1.0 equiv of **8** in THF at −78 °C, high yield of **50a** and 6*S*,7*R*-diastereoisomer **50b** (ca. 1.3:1.0 ratio of diastereoisomers); (b) 3.0 equiv of TBSOTf, 5.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h; (c) 2.0 equiv of K_2CO_3, MeOH, 25 °C, 15 min, 32% of **52** and 28% of 6*S*,7*R*-diastereoisomer **53** from **8**; (d) 6.0 equiv of TBAF, THF, 25 °C, 8 h, 73%; (e) same as d, 71%; (f) 5.0 equiv of 2,4,6-trichlorobenzoyl chloride, 6.0 equiv of Et_3N, THF, 25 °C, 15 min, then add to a solution of 10.0 equiv of 4-DMAP in toluene (0.002 M based on **6**), 25 °C, 12 h, 77%; (g) same as f, 76%; (h) 20% CF_3COOH (by volume) in CH_2Cl_2, 0 °C, 1 h, 91%; (i) see Scheme 7.

4. Conclusion

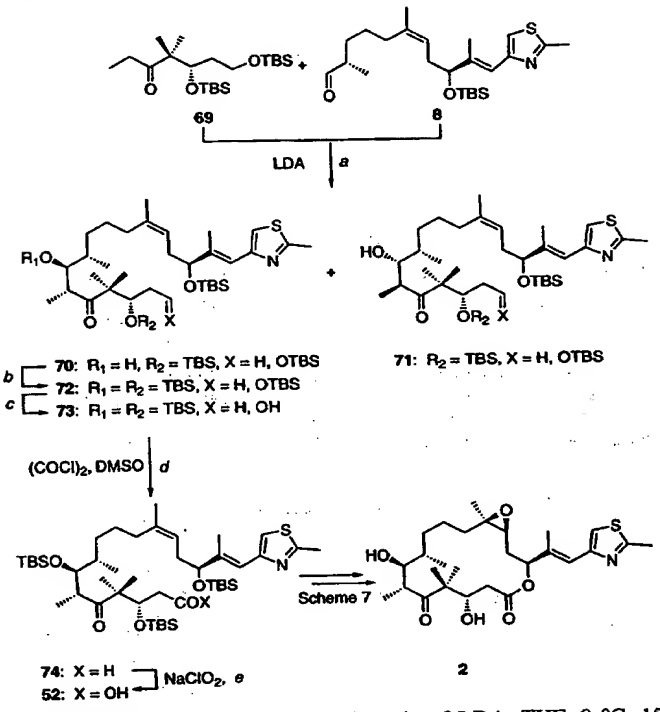
The chemistry described in this article defines a concise strategy for the construction of epothilones A (**1**) and B (**2**) based on a macrolactonization strategy, and which enjoys convergency and flexibility for structural diversity. It is expected that the numerous intermediates and structural analogues included herein, as well as several new ones currently under construction, will play a crucial role in elucidating structure–activity relationships of these new substances and in determining their relevance to cancer chemotherapy. Indeed, independent reports from the Danishefsky[8b,12] and from these laboratories[13] demonstrated impressive tubulin binding affinities and cytotoxicities for some of these compounds. Further details on the biological actions of these and other compounds will be published elsewhere.

Experimental Section

General Techniques. See preceding paper.[29]

Alcohol 18. Allylboration of Keto Aldehyde 17. Aldehyde **17**[16] (16.0 g, 0.125 mol) was dissolved in ether (400 mL) and cooled to −100 °C. To this solution was added (+)-diisopinocampheylallylborane (800 mL, 0.15 M in pentane, 0.125 mol, 1.0 equiv) by cannulation during 45 min. [(+)-Diisopinocampheylallylborane in pentane was typically prepared by the adaptation of the original method reported by Brown.[14] Allylmagnesium bromide (66.0 mL, 1 M solution in ether,

Scheme 10. Second Stereoselective Synthesis of Epothilone B (2)[a]



[a] Reagents and conditions: (a) 1.2 equiv of LDA, THF, 0 °C, 15 min; then 1.2 equiv of **69** in THF, −78 → −40 °C, 1 h; then 1.0 equiv of **8** in THF at −78 °C, 85% of **70** and 6*S*,7*R*-diastereoisomer **71** (ca. 3:1 ratio); (b) 1.2 equiv of TBSOTf, 2.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 96%; (c) 1.0 equiv of CSA portionwise over 1 h, CH_2Cl_2:MeOH (1:1), 0 → 25 °C, 0.5 h, 85%; (d) 2.0 equiv of $(COCl)_2$, 4.0 equiv of DMSO, 6.0 equiv of Et_3N, CH_2Cl_2, −78 → 0 °C, 1.5 h, 95%; (e) 3.0 equiv of $NaClO_2$, 4.0 equiv of 2-methyl-2-butene, 1.5 equiv of NaH_2PO_4, ^{t}BuOH:H_2O (5:1), 25 °C, 2 h, 90%.

0.066 mol) was added dropwise to a well-stirred solution of (−)-*B*-methoxydiisopinocampheylborane (20.9 g, 0.066 mol) in ether (400 mL) at 0 °C. After the completion of the addition, the reaction mixture was stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The residue was extracted with pentane (3 × 400 mL) under argon, and stirring was discontinued to allow precipitation of the magnesium salts. The clear pentane solution was cannulated into another flask using a double-ended needle through a Kramer filter and used without further purification. After the addition was complete, the mixture was stirred at the same temperature for 30 min. Methanol (20 mL) was added at −100 °C, and the reaction mixture was allowed to reach room temperature. To this solution was added saturated aqueous $NaHCO_3$ solution (200 mL), followed by H_2O_2 (80 mL of 50% solution in H_2O), and the reaction mixture was allowed to stir at room temperature for 12 h. The reaction mixture was extracted with EtOAc (3 × 200 mL), and the organic extracts were combined, washed with saturated aqueous NH_4Cl solution (100 mL), and dried (Na_2SO_4). Evaporation of the solvents followed by flash column chromatography (silica gel, 3% acetone in CH_2Cl_2) resulted in pure alcohol **18** (14.6 g, 74%). **18**: colorless oil; R_f = 0.20 (silica gel, 3% acetone in CH_2Cl_2); $[\alpha]^{22}_D$ −4.0 (*c* 1.5, $CHCl_3$); IR (thin film) ν_{max} 3492, 2976, 2939, 1699, 1641, 1469, 1379, 1087, 1020, 990, 973, 914 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85−5.80 (m, 1 H, C*H*=CH$_2$), 5.11−5.07 (m, 2 H, CH=C*H*$_2$), 3.73 (dd, J = 10.5, 2.0 Hz, 1 H, C*H*OH), 2.54−2.40 (m, 3 H), 2.25−2.18 (m, 1 H), 2.03−1.96 (m, 1 H), 1.14 (s, 3 H, C(C*H*$_3$)$_2$), 1.10 (s, 3 H, C(C*H*$_3$)$_2$), 0.99 (t, J = 7.0 Hz, 3 H, C*H*$_3$CH$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 217.2, 135.6, 117.7, 75.5, 51.2, 36.4, 31.3, 21.8, 19.5, 7.8; FAB HRMS (NBA/NaI) *m/e* 193.1200, M + Na$^+$ calcd for $C_{10}H_{18}O_2$ 193.1204.

Ketone 19. Silylation of Alcohol 18. Alcohol **18** (11.0 g, 0.0647 mol) was dissolved in CH_2Cl_2 (200 mL), the solution was cooled at −78 °C, and 2,6-lutidine (10.5 mL, 0.0906 mol, 1.4 equiv) was added. After being stirred for 5 min at that temperature, *tert*-butyldimethylsilyl triflate (19.3 mL, 0.0841 mol, 1.3 equiv) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 45 min, after which time no starting material was detected by TLC. Saturated aqueous NH_4Cl solution (30 mL) was added, and the reaction mixture was allowed to warm to room temperature. The organic phase was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and filtered through Celite, and the solvents were removed under reduced pressure. Purification by flash column chromatography (silica gel, 2 → 10% ether in hexanes) gave pure **19** (18.0 g, 98%): R_f = 0.75 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ +2.6 (*c* 0.8, $CHCl_3$); IR (thin film) ν_{max} 2935, 1705, 1467, 1362, 1254, 1089, 911, 836, 775 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78−5.71 (m, 1 H, C*H*=CH$_2$), 5.01−4.94 (m, 2 H, CH=C*H*$_2$), 3.97 (dd, J = 6.2, 5.2 Hz, 1 H, CHOSi), 2.54 (dq, J = 14.3, 7.2 Hz, 1 H, C*H*$_2$CH$_3$), 2.44 (dq, J = 14.2, 7.1 Hz, 1 H, C*H*$_2$CH$_3$), 2.21−2.16 (m, 1 H, C*H*$_2$CH=CH$_2$), 2.14−2.08 (m, 1 H, C*H*$_2$CH=CH$_2$), 1.10 (s, 3 H, C(CH$_3$)$_2$), 1.07 (s, 3 H, C(CH$_3$)$_2$), 0.98 (t, J = 7.1 Hz, 3 H, C*H*$_3$CH$_2$), 0.87 (s, 9 H, SiC(CH$_3$)$_3$), 0.05 (s, 3 H, Si(CH$_3$)$_2$), 0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 215.9, 136.2, 116.5, 76.7, 52.9, 39.0, 31.9, 26.0, 22.4, 20.1, 18.2, 7.7, −3.6, −4.4.

Keto Aldehyde 20. Ozonolysis of Ketone 19. Alkene **19** (2.84 g, 10 mmol) was dissolved in CH_2Cl_2 (25 mL, 0.4 M), and the solution was cooled to −78 °C. Oxygen was bubbled through for 2 min, after which time ozone was passed through until the reaction mixture adopted a blue color (ca. 30 min). The solution was then purged with oxygen for 2 min at −78 °C (disappearance of blue color) and Ph_3P (3.16 g, 12.0 mmol, 1.2 equiv) was added. The cooling bath was removed, and the reaction mixture was allowed to reach room temperature and stirred for an additional 1 h. The solvent was removed under reduced pressure, and the mixture was purified by flash column chromatography (silica gel, 25% ether in hexanes) to provide pure keto aldehyde **20** (2.57 g, 90%): R_f = 0.45 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ −1.9 (*c* 4.0, $CHCl_3$); IR (thin film) ν_{max} 2935, 2858, 1707, 1467, 1388, 1255, 1093, 1004, 837, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (dd, J = 2.1, 2.0 Hz, CHO), 4.55 (dd, J = 6.0, 4.5 Hz, 1 H, CHOSi), 2.59−2.44 (m, 4 H, C*H*$_2$CH$_3$, C*H*$_2$CH=O), 1.13 (s, 3 H, C(CH$_3$)$_2$), 1.09 (s, 3 H, C(CH$_3$)$_2$), 1.00 (t, J = 7.0 Hz, 3 H, C*H*$_3$CH$_2$), 0.85 (s, 9 H, (CH$_3$)$_3$C), 0.06 (s, 3 H, Si(CH$_3$)$_2$), 0.03 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 215.3, 200.9, 71.3, 52.3, 48.5, 31.9, 25.8, 21.3, 20.4, 18.0, 7.5, −4.4, −4.9; FAB HRMS (NBA/NaI) *m/e* 309.1854, M + Na$^+$ calcd for $C_{15}H_{30}O_3Si$ 309.1862.

Keto Acid 9. Oxidation of Keto Aldehyde 20. Aldehyde **20** (2.86 g, 10 mmol), ^{t}BuOH (50 mL, 0.2 M), isobutylene (20 mL, 2 M solution in THF, 40 mmol, 4.0 equiv), H_2O (10 mL), $NaClO_2$ (2.71 g, 30.0 mmol, 3.0 equiv), and NaH_2PO_4 (1.80 g, 15.0 mmol, 1.5 equiv) were combined and stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash column chromatography (silica gel, 50% ether in hexanes) to produce pure keto acid **9** (2.81 g, 93%): R_f = 0.12 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ +16.1 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2934, 2858, 1710, 1467, 1254, 1093, 834 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.46 (dd, J = 7.0, 3.6 Hz, 1 H, CHOSi), 2.64−2.34 (m, 3 H, C*H*$_2$CH$_3$, C*H*$_2$COOH), 2.32 (q, J = 7.0 Hz, 1 H, C*H*$_2$CH$_3$), 1.13 (s, 3 H, C(CH$_3$)$_2$), 1.11 (s, 3 H, C(CH$_3$)$_2$), 0.99 (t, J = 7.0 Hz, 3 H, C*H*$_3$CH$_2$), 0.83 (s, 9 H, (CH$_3$)$_3$C), 0.04 (s, 3 H, Si(CH$_3$)$_2$), 0.03 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 215.1, 178.2, 73.4, 52.4, 39.2, 31.6, 25.8, 20.8, 20.5, 18.0, 7.6, −4.5, −5.0; FAB HRMS (NBA) *m/e* 303.1996, M + H$^+$ calcd for $C_{15}H_{30}O_3Si$ 303.1992.

Aldehyde 22. Reduction of Ester 21. Ethyl ester **21**[18] (52.5 g, 0.306 mol) was dissolved in CH_2Cl_2 (1 L) and cooled to −78 °C. DIBAL (490.0 mL, 1 M solution in CH_2Cl_2, 0.4896 mol, 1.6 equiv) was added dropwise via a cannula while the temperature of the reaction mixture was maintained at −78 °C. After the addition was complete, the reaction mixture was stirred at the same temperature until its completion was verified by TLC (ca. 1 h). Methanol (100 mL) was added at −78 °C and was followed by addition of EtOAc (1 L) and saturated aqueous NH_4Cl solution (300 mL). The quenched reaction mixture was allowed to warm to room temperature and stirred for 12 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 200 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 10 → 90% ether in hexanes) furnished the desired aldehyde **22** (33.6 g, 90%): R_f =

0.68 (silica gel, ether); IR (thin film) ν_{max} 3095, 2828, 1695, 1485, 1437, 1378, 1334, 1178, 1129, 1011 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1 H, CHO), 8.0 (s, 1 H, SCH=C), 2.77 (s, 3 H, N=C(S)-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 184.2, 167.5, 154.8, 128.0, 19.1; FAB HRMS (NBA/NaI) *m/e* 149.9992, M + Na$^+$ calcd for C_5H_5-NOS 149.9990.

Aldehyde 23. Aromatic aldehyde **22** (31.1 g, 0.245 mol) was dissolved in benzene (500 mL), and 2-(triphenylphosphoranilidenyl)-propionaldehyde (90.0 g, 0.282 mol, 1.15 equiv) was added. The reaction mixture was heated at reflux until the reaction was complete as judged by TLC (ca. 2 h). Evaporation of the solvent under reduced pressure followed by flash column chromatography (10 → 90% ether in hexanes) produced the desired aldehyde **23** (40.08 g, 98%): R_f = 0.78 (silica gel, ether); IR (thin film) ν_{max} 3089, 1675, 1624, 1190, 1141, 1029, 947.6, 881 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1 H, CHO), 7.46 (s, 1 H), 7.26 (s, 1 H), 2.77 (s, 3 H, N=C(S)CH_3), 2.20 (s, 3 H, CH=C(CHO)CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 195.3, 165.7, 151.9, 140.9, 138.2, 122.6, 19.2, 10.9; FAB HRMS (NBA) *m/e* 168.0481, M + H$^+$ calcd for C_8H_9NOS 168.0483.

Alcohol 24. Allylboration of Aldehyde 23. Aldehyde **23** (20.0 g, 0.120 mol) was dissolved in anhydrous ether (400 mL), and the solution was cooled to −100 °C. (+)-Diisopinocampheylallylborane (1.5 equiv in pentane, prepared from 60.0 g of (−)-Ipc_2BOMe and 1.0 equiv of allylmagnesium bromide according to the method described for the synthesis of alcohol **18**),[14] was added dropwise under vigorous stirring, and the reaction mixture was allowed to stir for 1 h at the same temperature. Methanol (40 mL) was added at −100 °C, and the reaction mixture was allowed to warm to room temperature. Aminoethanol (72.43 mL, 1.2 mol, 10.0 equiv) was added, and stirring was continued for 15 h. The workup procedure was completed by the addition of saturated aqueous NH_4Cl solution (200 mL), extraction with EtOAc (4 × 100 mL), and drying of the combined organic layers with $MgSO_4$. Filtration followed by evaporation of the solvents under reduced pressure and flash column chromatography (silica gel, 35% ether in hexanes for several fractions until all the boron complexes were removed; then 70% ether in hexanes) provided alcohol **24** (24.09 g, 96%): R_f = 0.37 (60% ether in hexanes); $[\alpha]^{22}_D$ −20.2 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3357, 2923, 1642, 1505, 1437, 1322, 1186, 1018, 914, 878 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.81 (s, 1 H, SCH=C), 6.46 (s, 1 H, C*H*=CCH$_3$), 5.87−5.79 (m, 1 H, C*H*=CH$_2$), 5.02 (d, *J* = 17.1 Hz, 1 H, CH=C*H*$_2$), 4.97 (d, *J* = 10.3 Hz, 1 H, CH=C*H*$_2$), 4.12 (dd, *J* = 7.8, 5.0 Hz, 1 H, C*H*OH), 3.8 (bs, 1 H, OH), 2.59 (s, 3 H, N=C(S)CH$_3$), 2.31 (dd, *J* = 7.0, 6.5 Hz, 2 H, CH$_2$=CHC*H*$_2$), 1.91 (s, 3 H, CH=CC*H*$_3$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.5, 152.5, 141.8, 134.8, 118.7, 117.1, 115.1, 76.3, 39.8, 18.8, 14.1; FAB HRMS (NBA) *m/e* 210.0956, M + H$^+$ calcd for $C_{11}H_{15}NOS$ 210.0953.

Compound 25. Silylation of Alcohol 24. Alcohol **24** (7.0 g, 0.033 mol) was dissolved in DMF (35 mL, 1.0 M), the solution was cooled to 0 °C, and imidazole (3.5 g, 0.050 mol, 1.5 equiv) was added. After stirring for 5 min, *tert*-butyldimethylsilyl chloride (6.02 g, 0.040 mol, 1.2 equiv) was added portionwise and the reaction mixture was allowed to stir at 0 °C for 45 min, and then at 25 °C for 2.5 h, after which time no starting alcohol was detected by TLC. Methanol (2 mL) was added at 0 °C, and the solvent was removed under reduced pressure. Ether (100 mL) was added followed by saturated aqueous NH_4Cl solution (20 mL), the organic phase was separated, and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic solution was dried ($MgSO_4$) and filtered over Celite, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 10 → 20% ether in hexanes) provided pure **25** (10.8 g, 99%): R_f = 0.70 (40% ether in hexanes); $[\alpha]^{22}_D$ +1.39 (*c* 3.0, $CHCl_3$); IR (thin film) ν_{max} 2931, 2060, 1496, 1460, 1249, 1173, 1073, 908, 837, 779 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H, C*H*=CCH$_3$), 5.80−5.75 (m, 1 H, C*H*=CH$_2$), 5.03 (ddd, *J* = 17.1, 3.5, 1.5 Hz, 1 H, CH=C*H*$_2$), 4.99 (ddd, *J* = 10.2, 2.1, 0.9 Hz, 1 H, CH=C*H*$_2$), 4.14 (dd, *J* = 6.6, 6.1 Hz, 1 H, C*H*OH), 2.69 (s, 3 H, N=C-(S)CH$_3$), 2.37−2.32 (m, 1 H, CH$_2$=CHC*H*$_2$), 2.31−2.25 (m, 1 H, CH$_2$=CHC*H*$_2$), 1.99 (s, 3 H, CH=CC*H*$_3$), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.05 (s, 3 H, Si(CH$_3$)$_2$), 0.00 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 165.2, 153.9, 142.9, 136.2, 119.7, 117.4, 115.9, 79.3, 42.1, 26.7, 20.1, 19.0, 14.8, −3.8, −4.1; FAB HRMS (NBA) *m/e* 324.1804, M + H$^+$ calcd for $C_{17}H_{29}NOSSi$ 324.1817.

Aldehyde 15. Dihydroxylation of Olefin 25 and 1,2 Glycol Cleavage. Olefin **25** (16.7 g, 51.6 mmol) was dissolved in THF/^{t}-BuOH (1:1, 500 mL) and H_2O (50 mL). 4-Methylmorpholine *N*-oxide (NMO) (7.3 g, 61.9 mmol, 1.2 equiv) was added at 0 °C, followed by OsO_4 (5.2 mL, solution in ^{t}BuOH 1.0 mol %, 2.5% by weight). The mixture was vigorously stirred for 2.5 h at 0 °C and then for 12 h at 25 °C. After completion of the reaction, Na_2SO_3 (5.0 g) was added at 0 °C, followed by H_2O (100 mL). Stirring was continued for another 30 min, and then ether (1 L) was added, followed by saturated aqueous NaCl solution (2 × 100 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, ether → EtOAc) provided 17.54 g (95%) of the expected 1,2-diol as a 1:1 mixture of diastereoisomers: R_f = 0.55 (silica gel, EtOAc); IR (thin film) ν_{max} 3380, 2931, 2856, 1656, 1505, 1465, 1460, 1254, 1187, 1073, 908, 837, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 and 6.88 (singlets, 1 H total, SCH=C), 6.52 and 6.47 (singlets, 1 H total, C*H*=CCH$_3$), 4.44−4.39 (m, 1 H), 3.95−3.84 (m, 1 H), 3.81−3.72 and 3.63−3.34 (m, 4 H total), 2.66 and 2.65 (singlets, 3 H total, N=C(S)CH$_3$), 1.96 and 1.95 (singlets, 3 H total), 1.82−1.75 and 1.69−1.56 (m, 2 H total), 0.87 and 0.86 (singlets, 9 H total, SiC(CH$_3$)$_3$), 0.08 and −0.01 (singlets, 3 H total, Si(CH$_3$)$_2$), 0.07 and 0.10 (singlets, 3 H total, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.6, 164.5, 152.8, 152.4, 141.6, 141.5, 119.4, 118.4, 115.3, 115.2, 78.0, 75.4, 70.4, 68.8, 66.8, 66.5, 38.9, 38.7, 25.7, 19.0, 18.9, 18.0, 17.9, 14.6, 13.5, −4.6, −4.8, −5.2, −5.4; FAB HRMS (NBA/NaI) *m/e* 380.1699, M + Na$^+$ calcd for $C_{17}H_{31}NO_3SSi$ 380.1692.

The diol obtained from **25** as described above (5.2 g, 14.5 mmol) was dissolved in EtOAc (150 mL) and cooled to 0 °C. $Pb(OAc)_4$ (8.1 g, 95% purity, 18.3 mmol, 1.2 equiv) was then added portionwise over 10 min, and the mixture was vigorously stirred for 15 min at 0 °C. After completion of the reaction, the mixture was filtered through silica gel and washed with 60% ether in hexanes. The solvents were then removed under reduced pressure providing pure aldehyde **15** (4.7 g, 98%): R_f = 0.76 (silica gel, 60% ether in hexanes); $[\alpha]^{22}_D$ −20.3 (*c* 1.4, $CHCl_3$); IR (thin film) ν_{max} 2931, 2856, 1726, 1504, 1466, 1389, 1254, 1182, 1087, 999, 839, 784 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (dd, *J* = 2.7, 2.2 Hz, 1 H, CHO), 6.86 (s, 1 H, SCH=C), 6.48 (s, 1 H, C*H*=CCH$_3$), 4.60 (dd, *J* = 8.2, 3.9 Hz, 1 H, CHOSi), 2.64 (ddd, *J* = 15.5, 8.3, 2.9 Hz, 1 H, CHOC*H*$_2$), 2.59 (s, 3 H, N=C(S)CH$_3$), 2.41 (ddd, *J* = 15.5, 4.0, 2.0 Hz, 1 H, CHOC*H*$_2$), 1.95 (s, 3 H, CH=CC*H*$_3$), 0.79 (s, 9 H, SiC(CH$_3$)$_3$), 0.00 (s, 3 H, Si(CH$_3$)$_2$), −0.06 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 201.0, 164.5, 152.4, 140.3, 119.0, 115.8, 73.7, 49.9, 25.6, 18.9, 17.9, 13.9, −4.8, −5.4; FAB HRMS (NBA) *m/e* 326.1615, M + H$^+$ calcd for $C_{16}H_{27}NO_2SSi$ 326.1610.

Alcohol 26. Reduction of Aldehyde 15. A solution of aldehyde **15** (440 mg, 1.35 mmol) in MeOH (13 mL) was treated with $NaBH_4$ (74 mg, 2.0 mmol, 1.5 equiv) at 0 °C for 15 min. The solution was diluted with ether (100 mL), and then saturated aqueous NH_4Cl solution (5 mL) was carefully added. The organic phase was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica gel, 60% ether in hexanes) gave alcohol **26** (425 mg, 96%) as a colorless oil. **26**: R_f = 0.52 (silica gel, 60% ether in hexanes); $[\alpha]^{22}_D$ −29.4 (*c* 0.8, $CHCl_3$); IR (thin film) ν_{max} 3362, 2950, 2856, 1656, 1505, 1466, 1362, 1254, 1186, 1075, 839, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1 H, SCH=C), 6.40 (s, 1 H, C*H*=CCH$_3$), 4.30 (dd, *J* = 7.6, 5.3 Hz, 1 H, CHOSi), 3.69−3.59 (m, 2 H, C*H*$_2$OH), 3.15 (s, 1 H, OH), 2.61 (s, 3 H, N=C(S)CH$_3$), 1.92 (s, 3 H, CH=CC*H*$_3$), 1.82−1.76 (m, 1 H, C*H*$_2$CH$_2$OH), 1.73−1.67 (m, 1 H, C*H*$_2$CH$_2$OH), 0.82 (s, 9 H, SiC(CH$_3$)$_3$), 0.02 (s, 3 H, Si(CH$_3$)$_2$), −0.05 (s, 3 H, Si-(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.3, 152.7, 141.6, 118.5, 115.1, 76.6, 59.6, 38.3, 25.8, 18.9, 18.0, 14.0, −4.8, −5.4; FAB HRMS (NBA/CsI) *m/e* 460.0727, M + Cs$^+$ calcd for $C_{16}H_{29}NO_2SSi$ 460.0743.

Iodide 27. Iodination of Alcohol 26. A solution of alcohol **26** (14.0 g, 42.7 mmol) in ether: MeCN (3:1, 250 mL) was cooled to 0 °C. Imidazole (8.7 g, 128.1 mmol, 3.0 equiv), Ph_3P (16.8 g, 64.1 mmol, 1.5 equiv), and iodine (16.3 g, 64.1 mmol, 1.5 equiv) were sequentially added, and the mixture was stirred for 0.5 h at 0 °C. A saturated aqueous solution of $Na_2S_2O_3$ (50 mL) was added, followed by the addition of ether (600 mL). The organic phase was washed with brine (50 mL) and dried ($MgSO_4$), and the solvents were removed under

vacuum. Flash column chromatography (silica gel, 15% ether in hexanes) gave pure iodide **27** (16.6 g, 89%) as a colorless oil: R_f = 0.40 (silica gel, 10% ether in hexanes); $[\alpha]^{22}_D$ +11.0 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2951, 2856, 1503, 1466, 1253, 1179, 1081, 936, 884, 836, 777 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.90 (s, 1 H, SCH=C), 6.53 (s, 1 H, C*H*=CCH$_3$), 4.19 (dd, *J* = 7.7, 4.5 Hz, 1 H, CHOSi), 3.18 (t, *J* = 7.3 Hz, 2 H, CH_2I), 2.67 (s, 3 H, N=C(S)CH$_3$), 2.10−2.05 (m, 1 H, C*H*$_2$CH$_2$I), 2.01−1.95 (m, 1 H, CH$_2$C*H*$_2$I), 1.99 (s, 3 H, CH=CC*H*$_3$), 0.87 (s, 9 H, SiC(CH$_3$)$_3$), 0.09 (s, 3 H, Si(CH$_3$)$_2$), 0.00 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.4, 152.7, 140.9, 119.3, 115.4, 78.0, 40.2, 25.8, 19.2, 18.1, 13.9, 3.1, −4.6, −5.0; FAB HRMS (NBA) *m/e* 438.0768, M + H$^+$ calcd for $C_{16}H_{28}INOSSi$ 438.0784.

Phosphonium Salt 12. A mixture of iodide **27** (16.5 g, 37.7 mmol) and Ph_3P (10.9 g, 41.5 mmol, 1.1 equiv) was heated neat at 100 °C for 2 h. Purification by flash column chromatography (silica gel, CH_2Cl_2; then 7% MeOH in CH_2Cl_2) provided phosphonium salt **12** (25.9 g, 98%) as a white solid: R_f = 0.50 (silica gel, 7% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ +3.7 (*c* 0.7, $CHCl_3$); IR (thin film) ν_{max} 2951, 2856, 1503, 1466, 1253, 1179, 1081, 936, 884, 836, 777 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.78−7.28 (m, 15 H, aromatic), 6.97 (s, 1 H, SCH=C), 6.57 (s, 1 H, C*H*=CCH$_3$), 4.48 (dd, *J* = 6.3, 4.8 Hz, 1 H, CHOSi), 3.72−3.65 (m, 1 H, CH$_2$P), 3.31−3.25 (m, 1 H, CH$_2$P), 2.61 (s, 3 H, N=C-(S)CH$_3$), 1.91 (s, 3 H, CH=CC*H*$_3$), 1.95−1.86 (m, 1 H, C*H*$_2$CH$_2$P), 1.82−1.74 (m, 1 H, C*H*$_2$CH$_2$ P), 0.83 (s, 9 H, SiC(CH$_3$)$_3$), 0.07 (s, 3 H, Si(CH$_3$)$_2$), −0.02 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.4, 152.3, 139.4, 135.1, 133.3, 133.2, 130.5, 130.4, 128.1, 119.8, 117.9, 117.3, 116.5, 76.0, 28.9, 25.7, 19.1, 18.4, 17.9, 14.5, −4.8.

Hydrazone 28. Alkylation of Hydrazone 13. Hydrazone **13**[15] (20.0 g, 117.0 mmol, 1.0 equiv), dissolved in THF (80 mL), was added to a freshly prepared solution of LDA [19.75 mL of diisopropylamine (141.0 mmol, 1.2 equiv) was added to a solution of 88.1 mL of 1.6 M solution of *n*-BuLi in hexanes (141 mmol, 1.2 equiv) in 160 mL of THF at 0 °C] at 0 °C. After the mixture was stirred at this temperature for 8 h, the resulting yellow solution was cooled to −100 °C and a solution of 4-iodo-1-(benzyloxy)butane (36.0 g, 124.0 mmol, 1.2 equiv) in THF (40 mL) was added dropwise over a period of 30 min. The mixture was allowed to warm to room temperature over 8 h and was then poured into saturated aqueous NH_4Cl solution (40 mL) and extracted with ether (3 × 200 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Purification by flash column chromatography on silica gel (20% ether in hexanes) provided hydrazone **28** as a yellow oil (35.8 g, 92%, de > 98% by ^1H NMR): R_f = 0.45 (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ −55.0 (*c* 1.2, $CHCl_3$); IR (thin film) ν_{max} 2929, 2862, 1603, 1455, 1362, 1198, 1108, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (s, 5 H, Ph), 6.48 (d, *J* = 6.5 Hz, 1 H, CH=NN), 4.46 (s, 2 H, CH_2Ph), 3.54 (dd, *J* = 9.0, 3.8 Hz, 1 H, C*H*$_2$OCH$_3$), 3.44 (t, *J* = 6.5 Hz, 2 H, CH$_2$OBn), 3.40 (dd, *J* = 9.0, 6.8 Hz, 1 H, C*H*$_2$OCH$_3$), 3.33 (s, 3 H, OCH$_3$), 2.65 (m, 1 H, C*H*CH$_2$OCH$_3$), 2.29 (m, 1 H, C*H*(CH$_3$)C=N), 1.94−1.76 (m, 4 H), 1.61 (m, 2 H), 1.45−1.36 (m, 6 H), 1.01 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 144.6, 138.6, 128.2, 127.5, 127.3, 74.7, 72.7, 70.2, 63.4, 59.1, 50.4, 37.0, 35.2, 29.7, 26.4, 23.7, 22.0, 18.9; FAB HRMS (NBA) *m/e* 333.2552, M + H$^+$ calcd for $C_{20}H_{32}N_2O_2$ 333.2542.

Aldehyde 29. Cleavage of Hydrazone 28. Procedure A: A solution of hydrazone **28** (13.0 g, 39.1 mmol) in CH_2Cl_2 (50 mL) was treated with ozone at −78 °C until the solution turned blue-green. The solution was purged with oxygen for 2 min at −78 °C, allowed to warm to room temperature, and then concentrated. The crude mixture so obtained was purified by flash column chromatography (silica gel, 10% ether in hexanes) to give aldehyde **29** (6.6 g, 77%) as a colorless oil. **Procedure B:** A solution of hydrazone **28** (30 g, 90.3 mmol) in MeI (100 mL) was heated at 60 °C. After 5 h, the reaction was complete (TLC) and the mixture was concentrated. The resulting crude product was suspended in *n*-pentane (360 mL) and was treated with 3 N aqueous HCl (360 mL). The two-phase system was vigorously stirred for 1 h, and the aqueous phase was extracted with *n*-pentane (3 × 200 mL). The combined organic solution was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, 10% ether in hexanes) to give **29** (17.1 g, 86%): R_f = 0.49 (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ +11.6 (*c* 1.7, $CHCl_3$); IR (thin film) ν_{max} 2932, 2856, 1715, 1459, 1361, 1272, 1202, 1102, 920, 732, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, *J* = 2.0 Hz, 1 H, CHO), 7.34 (s, 5 H, Ph), 4.50 (s, 2 H, CH_2Ph), 3.47 (t, *J* = 6.5 Hz, 2 H, CH$_2$OBn), 2.33 (m, 1 H, C*H*(CH$_3$)CO), 1.75−1.69 (m, 1 H), 1.65−1.61 (m, 2 H), 1.49−1.34 (m, 3 H), 1.08 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 205.0, 138.4, 128.2, 127.5, 127.4, 72.8, 69.9, 46.1, 30.1, 29.6, 23.6, 13.2; FAB HRMS (NBA) *m/e* 221.1538, M + H$^+$ calcd for $C_{14}H_{20}O_2$ 221.1542.

Alcohol 30. Reduction of Aldehyde 29. A solution of aldehyde **29** (17.0 g, 77.0 mmol) in MeOH (200 mL) was treated with $NaBH_4$ (8.6 g, 228 mmol, 3.0 equiv) at 0 °C for 15 min. The solution was then diluted with ether (400 mL), and saturated aqueous NH_4Cl solution (50 mL) was carefully added. The organic phase was washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography (silica gel, 40% ether in hexanes) to give alcohol **30** (16.8 g, 98%) as a colorless oil: R_f = 0.23 (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ −5.1 (*c* 1.9, $CHCl_3$); IR (thin film) ν_{max} 3401, 2931, 2860, 1455, 1361, 1267, 1202, 1102, 1037, 937, 732, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 5 H, Ph), 4.51 (s, 2 H, CH_2Ph), 3.50 (dd, *J* = 11.0, 6.0 Hz, 1 H, C*H*$_2$OH), 3.48 (t, *J* = 6.5 Hz, 2 H, CH$_2$OBn), 3.42 (dd, *J* = 11.0, 6.5 Hz, 1 H, C*H*$_2$-OH), 1.65−1.59 (m, 2 H), 1.47−1.34 (m, 4 H), 1.15−1.12 (m, 1 H), 0.91 (d, *J* = 6.7 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.6, 128.2, 127.6, 127.3, 72.9, 70.3, 68.1, 35.7, 32.9, 30.1, 23.6, 14.1; FAB HRMS (NBA) *m/e* 223.1705, M + H$^+$ calcd for $C_{14}H_{22}O_2$ 223.1698.

Silyl Ether 31. Silylation of Alcohol 30. Alcohol **30** (17.0 g, 76.0 mmol) was dissolved in CH_2Cl_2 (350 mL), the solution was cooled to 0 °C and Et_3N (21.2 mL, 152.0 mmol, 2.0 equiv) and 4-DMAP (185 mg, 1.52 mmol, 0.05 equiv) were added. After the mixture was stirred for 5 min, *tert*-butyldimethylsilyl chloride (17.3 g, 115 mmol, 1.5 equiv) was added portionwise and the reaction mixture was allowed to stir at 0 °C for 2 h and then at 25 °C for 10 h. Methanol (20 mL) was added at 0 °C, and the solvents were removed under reduced pressure. Ether (200 mL) and saturated aqueous NH_4Cl solution (30 mL) were sequentially added, and the organic phase was separated. The aqueous phase was extracted with ether (2 × 100 mL), and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% ether in hexanes) provided pure silyl ether **31** (24.4 g, 95%): R_f = 0.54 (silica gel, 10% ether in hexanes); $[\alpha]^{22}_D$ −2.3 (*c* 1.1, $CHCl_3$); IR (thin film) ν_{max} 2931, 2860, 1461, 1361, 1249, 1091, 839, 773, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 5 H, Ph), 4.51 (s, 2 H, CH_2Ph), 3.48 (t, *J* = 6.5 Hz, 2 H, CH$_2$OBn), 3.43 (dd, *J* = 10.5, 6.0 Hz, 1 H, CH$_2$OSi), 3.36 (dd, *J* = 10.5, 6.5 Hz, 1 H, CH$_2$OSi), 1.64−1.60 (m, 3 H), 1.47−1.29 (m, 3 H), 1.15−1.05 (m, 1 H), 0.90 (s, 9 H, SiC(CH$_3$)$_3$), 0.87 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$), 0.043 (s, 3 H, Si(CH$_3$)$_2$), 0.041 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.6, 128.2, 127.5, 127.3, 72.7, 70.3, 68.3, 35.6, 32.9, 30.0, 25.8, 23.5, 18.1, 16.6, −5.5; FAB HRMS (NBA) *m/e* 337.2553, M + H$^+$ calcd for $C_{20}H_{36}O_2Si$ 337.2563.

Alcohol 32. Hydrogenolysis of Benzyl Ether 31. To a solution of benzyl ether **31** (21.0 g, 62.5 mmol) in THF (200 mL) was added 10% $Pd(OH)_2/C$ (1.0 g). The reaction was allowed to proceed under an atmosphere of H_2 at a pressure of 50 psi and at 25 °C (Parr hydrogenetor apparatus). After 15 min, no starting benzyl ether was detected by TLC and the mixture was filtered through Celite. The clear solution was concentrated under reduced pressure, and the resulting crude product was purified by flash column chromatography (silica gel, 40% ether in hexanes) to give alcohol **32** (14.7 g, 95%) as a colorless oil: R_f = 0.32 (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ −3.6 (*c* 3.6, $CHCl_3$); IR (thin film) ν_{max} 3342, 2931, 2860, 1467, 1384, 1249, 1085, 838, 773, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.63 (t, *J* = 7.0 Hz, 2 H, C*H*$_2$OH), 3.42 (dd, *J* = 11.0, 6.0 Hz, 1 H, CH$_2$OSi), 3.35 (dd, *J* = 11.0, 7.0 Hz, 1 H, CH$_2$OSi), 1.57−1.53 (m, 3 H), 1.42−1.39 (m, 3 H), 1.16−1.06 (m, 1 H), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.85 (d, *J* = 6.5 Hz, 3 H, CHC*H*$_3$), 0.03 (s, 3 H, Si(CH$_3$)$_2$), 0.02 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 68.2, 62.7, 35.6, 32.9, 32.8, 25.7, 23.0, 18.2, 16.5, −5.5; FAB HRMS (NBA) *m/e* 247.2097, M + H$^+$ calcd for $C_{13}H_{30}O_2Si$ 247.2093.

Aldehyde 10. Oxidation of Alcohol 32. To a solution of oxalyl chloride (5.6 mL, 65.0 mmol, 2.0 equiv) in CH_2Cl_2 (250 mL) was added dropwise DMSO (9.2 mL, 130 mmol, 4.0 equiv) at −78 °C. After the mixture was stirred for 15 min, a solution of alcohol **32** (8.0 g, 32.0

mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added dropwise at −78 °C over a 15 min period. The solution was stirred for a further 30 min at −78 °C, and Et_3N (27.1 mL, 194 mmol, 6.0 equiv) was added at the same temperature. The reaction mixture was allowed to warm to 0 °C over 30 min, and then ether (400 mL) was added, followed by saturated aqueous NH_4Cl solution (100 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2 × 300 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided aldehyde **10** (7.9 g, 98%) as a colorless oil: $R_f = 0.64$ (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ −5.1 (*c* 0.7, $CHCl_3$); IR (thin film) ν_{max} 2952, 2858, 1728, 1466, 1389, 1254, 1095, 841, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, J = 1.5 Hz, 1 H, CHO), 3.39 (dd, J = 9.8, 6.1 Hz, 1 H, CH_2OSi), 3.36 (dd, J = 9.8, 6.3 Hz, 1 H, CH_2OSi), 2.39 (m, 2 H, CH_2CHO), 171−1.64 (m, 1 H), 1.61−1.53 (m, 2 H), 1.44−1.38 (m, 1 H), 1.11−1.05 (m, 1 H), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.85 (d, J = 6.5 Hz, 3 H, $CHCH_3$), 0.019 (s, 3 H, $Si(CH_3)_2$), 0.004 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 202.7, 68.9, 44.1, 35.5, 32.6, 25.8, 23.0, 18.2, 16.5, −5.5; FAB HRMS (NBA) *m/e* 245.1932, M + H^+ calcd for $C_{13}H_{28}O_2Si$ 245.1937.

Alcohol 33. To a cold (0 °C) solution of aldehyde **10** (7.8 g, 32.0 mmol) in THF (300 mL) was slowly added MeMgBr (1.0 M solution in THF, 48.0 mL, 48.0 mmol, 1.5 equiv). The reaction mixture was stirred for 15 min at 0 °C, and then it was diluted with ether (500 mL) and quenched by carefull addition of saturated aqueous NH_4Cl solution (100 mL). The organic phase was washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The crude product so obtained was purified by flash column chromatography (silica gel, 30% ether in hexanes) to give alcohol **33** (7.0 g, 84%) as a colorless oil: $R_f = 0.38$ (silica gel, 50% ether in hexanes); IR (thin film) ν_{max} 3352, 2931, 2858, 1465, 1384, 1253, 1096, 839, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.79 (m, 1 H, $CH(CH_3)OH$), 3.43 (dd, J = 9.8, 6.0 Hz, 1 H, CH_2OSi), 3.36 (dd, J = 9.8, 6.8 Hz, 1 H, CH_2OSi), 1.61−1.57 (m, 1 H), 1.47−1.35 (m, 4 H), 1.30−1.26 (m, 1 H), 1.19 (d, J = 6.1 Hz, 3 H, $CH(OH)CH_3$), 1.09−1.05 (m, 1 H), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.86 (d, J = 6.7 Hz, 3 H, $CHCH_3$), 0.04 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 68.2, 67.9, 39.5, 35.6, 33.0, 25.9, 23.4, 23.1, 18.2, 16.6, −5.4; FAB HRMS (NBA) *m/e* 261.2256, M + H^+ calcd for $C_{14}H_{32}O_2Si$ 261.2250.

Ketone 11. Oxidation of Alcohol 33. To a solution of alcohol **33** (7.0 g, 27.0 mmol) in CH_2Cl_2 (250 mL) were added molecular sieves (4 Å, 6.0 g), 4-methylmorpholine *N*-oxide (NMO) (4.73 g, 40.0 mmol, 1.5 equiv), and tetrapropylammonium perruthenate (TPAP) (189 mg, 0.54 mmol, 0.02 equiv) at room temperature. After being stirred for 45 min (depletion of starting material, TLC), the reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% ether in hexanes) to give ketone **11** (6.6 g, 96%) as a colorless oil: $R_f = 0.67$ (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ −4.5 (*c* 1.1, $CHCl_3$); IR (thin film) ν_{max} 2931, 2849, 1713, 1461, 1355, 1249, 1161, 1091, 838, 773, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.41 (dd, J = 9.8, 6.0 Hz, 1 H, CH_2OSi), 3.36 (dd, J = 9.8, 6.3 Hz, 1 H, CH_2OSi), 2.41 (m, 2 H, CH_2COCH_3), 2.13 (s, 3 H, $COCH_3$), 168−1.48 (m, 3 H), 1.42−1.35 (m, 1 H), 1.09−1.00 (m, 1 H), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.86 (d, J = 6.7 Hz, 3 H, $CHCH_3$), 0.03 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 209.8, 68.0, 43.9, 35.5, 32.6, 29.7, 25.8, 21.2, 18.2, 16.4, −5.5; FAB HRMS (NBA) *m/e* 259.2097, M + H^+ calcd for $C_{14}H_{30}O_2Si$ 259.2093.

Iodide 46. Iodination of Alcohol 32. A solution of alcohol **32** (3.8 g, 15.0 mmol) in ether:MeCN, 3:1 (150 mL), was cooled to 0 °C. Imidazole (3.1 g, 45.0 mmol, 3.0 equiv), Ph_3P (5.9 g, 22.5 mmol, 1.5 equiv), and iodine (5.7 g, 22.5 mmol, 1.5 equiv) were sequentially added, and the reaction mixture was stirred at 0 °C for 0.5 h. A saturated aqueous solution of $Na_2S_2O_3$ (200 mL) was added followed with ether (200 mL). The organic phase was washed with brine (200 mL) and dried ($MgSO_4$), and the solvents were removed under vacuum. The crude product was purified by flash column chromatography (silica gel, 10% ether in hexanes) to give pure iodide **46** (4.9 g, 91%) as a colorless oil: $R_f = 0.68$ (silica gel, 10% ether in hexanes); $[\alpha]^{22}_D$ −4.3 (*c* 1.2, $CHCl_3$); IR (thin film) ν_{max} 2929, 2860, 1461, 1386, 1248, 1090, 836, 774, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.42 (dd, J = 10.0, 6.5 Hz, 1 H, CH_2OSi), 3.38 (dd, J = 10.0, 6.0 Hz, 1 H, CH_2OSi), 3.19 (t, J = 7.0 Hz, 2 H, CH_2I), 1.85−1.78 (m, 2 H), 1.61−1.55 (m, 1 H), 1.47−1.33 (m, 3 H), 1.10−1.02 (m, 1 H, CH_2), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.87 (d, J = 6.7 Hz, 3 H, $CHCH_3$), 0.04 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 68.1, 35.4, 33.7, 31.8, 27.8, 25.8, 18.2, 16.5, 7.1, −5.5; FAB HRMS (NBA) *m/e* 229.1983, M − I^- calcd for $C_{13}H_{39}IOSi$ 229.1988.

Phosphonium Salt 47. A mixture of iodide **46** (4.7 g, 13.1 mmol) and Ph_3P (3.8 g, 14.4 mmol, 1.1 equiv) was heated neat at 100 °C for 2 h. Purification by flash column chromatography (silica gel, CH_2Cl_2 — 7% MeOH in CH_2Cl_2) provided phosphonium salt **47** (7.4 g, 91%) as a white solid: $R_f = 0.42$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −7.3 (*c* 1.5, $CHCl_3$); IR (thin film) ν_{max} 2931, 2849, 1578, 1461, 1431, 1243, 1184, 1102, 997, 914, 838, 720, 685, 532, 503 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82−7.77 (m, 9 H, Ph), 7.74−7.68 (m, 6 H, Ph), 3.62 (dt, J = 12.5, 8.0 Hz, 2 H, CH_2P), 3.34 (dd, J = 9.5, 6.5 Hz, 1 H, CH_2OSi), 3.30 (dd, J = 9.5, 6.5 Hz, 1 H, CH_2OSi), 1.69−1.55 (m, 4 H), 1.50−1.46 (m, 1 H), 1.39−1.32 (m, 1 H), 1.10−1.01 (m, 1 H), 0.83 (s, 9 H, $SiC(CH_3)_3$), 0.79 (d, J = 6.6 Hz, 3 H, $CHCH_3$), −0.04 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 135.0, 133.6, 133.5, 133.2, 130.5, 130.4, 68.0, 35.2, 32.4, 27.8, 25.8, 23.2, 22.7, 18.2, 16.4, −5.5.

Olefin 34. Method A. From Phosphonium Salt 12 and Aldehyde 10: Phosphonium salt **12** (13.60 g, 19.4 mmol, 1.2 equiv) was dissolved in THF (80 mL, 0.2 M), and the solution was cooled to 0 °C. Sodium hexamethyldisilylamide (NaHMDS, 19.4 mL, 19.4 mmol, 1.0 M solution in THF, 1.2 equiv) was slowly added, and the resulting mixture was stirred for 15 min before aldehyde **10** (3.96 g, 16.2 mmol, 1.0 equiv, in 10 mL of THF) was added at the same temperature. Stirring was continued for another 15 min at 0 °C, and then, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (25 mL). Ether (250 mL) was added, and the organic phase was separated and washed with brine (2 × 40 mL), dried ($MgSO_4$), and concentrated under *vacuo*. The crude product was purified by flash column chromatography (silica gel, 10% ether in hexane) to afford olefin **34** (6.70 g, 77%) as a mixture of *Z*- and *E*-isomers (ca. 9:1 by ^1H NMR). **Method B. From Phosphonium Salt 47 and Aldehyde 15:** Phosphonium salt **47** (7.40 g, 11.96 mmol, 1.2 equiv) was dissolved in THF (120 mL, 0.1 M), and the solution was cooled to 0 °C. Sodium hexamethyldisilylamide (NaHMDS, 11.96 mL, 11.96 mmol, 1.0 M solution in THF, 1.2 equiv) was slowly added at the same temperature, and the resulting mixture was stirred for 15 min, before aldehyde **15** (3.20 g, 9.83 mmol, 1.0 equiv, in 20 mL of THF) was slowly added. Stirring was continued for another 15 min at 0 °C, and then the mixture was quenched with saturated aqueous NH_4Cl solution (150 mL). Ether (200 mL) was added, and the organic phase was separated and washed with brine (2 × 150 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude product. Flash column chromatography (silica gel, 10% ether in hexane) furnished olefin **34** (3.65 g, 69% yield) as a mixture of *Z*- and *E*-isomers (ca. 9:1 by ^1H NMR): $R_f = 0.75$ (silica gel, 50% ether in hexane); $[\alpha]^{22}_D$ +4.0 (*c* 0.5, $CHCl_3$); IR (thin film) ν_{max} 2930, 2856, 1465, 1388, 1253, 1089, 939, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (signals for the *Z*-isomer (**34**) only reported) δ 6.92 (s, 1 H, SCH=C), 6.46 (s, 1 H, $CH{=}CCH_3$), 5.49−5.31 (m, 2 H, CH=CH), 4.12 (dd, J = 6.5, 6.4 Hz, 1 H, CHOSi), 3.44 (dd, J = 9.8, 5.8 Hz, 1 H, CH_2OSi), 3.34 (dd, J = 9.8, 6.8 Hz, 1 H, CH_2OSi), 2.71 (s, 3 H, $N{=}C(S)CH_3$), 2.39−2.24 (m, 2 H, CH_2CHOSi), 2.00 (s, 3 H, $CH{=}CCH_3$), 2.05−1.96 (m, 2 H), 1.59−1.51 (m, 1 H), 1.42−1.23 (m, 3 H), 1.10−0.98 (m, 1 H), 0.89 (s, 18 H, $SiC(CH_3)_3$), 0.85 (d, J = 6.8 Hz, 3 H, CH_3CH), 0.06 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 6 H, $Si(CH_3)_2$), 0.01 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.3, 153.1, 142.2, 131.4, 125.7, 118.8, 114.9, 78.7, 68.3, 35.7, 34.6, 32.9, 27.8, 27.1, 25.9, 25.8, 19.2, 18.3, 18.2, 16.7, 13.9, −4.7, −4.9, −5.4; FAB HRMS (NBA) *m/e* 538.3582, M + H^+ calcd for $C_{29}H_{55}NO_2SSi_2$ 538.3570.

Alcohol 35. Compound **34** (1.77 g, 3.29 mmol) was dissolved in CH_2Cl_2:MeOH (1:1, 66 mL), the solution was cooled to 0 °C, and CSA (764 mg, 3.29 mmol, 1.0 equiv) was added over a 5 min period. The mixture was stirred for 30 min at 0 °C and then for 1 h at 25 °C. Et_3N (2.0 mL) was added, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 50% ether in hexanes) furnished the desired alcohol **35** (1.2 g, 86%): $R_f = 0.72$ (silica gel, 80% ether in hexanes); $[\alpha]^{22}_D$ +1.1 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3370, 2923, 2857, 1464, 1384, 1253, 1185, 1074, 836, 776

cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH=C), 6.44 (s, 1 H, C*H*=CCH$_3$), 5.45–5.32 (m, 2 H, CH=CH), 4.12 (dd, J = 6.5, 6.4 Hz, 1 H, CHOSi), 3.46 (dd, J = 10.5, 5.9 Hz, 1 H, C*H*$_2$OH), 3.37 (dd, J = 10.5, 6.5 Hz, 1 H, C*H*$_2$OH), 2.68 (s, 3 H, N=C(S)CH$_3$), 2.39–2.21 (m, 2 H, C*H*$_2$CHOSi), 2.21 (s, 1 H, OH), 1.98 (s, 3 H, CH=CC*H*$_3$), 2.05–1.95 (m, 2 H), 1.59–1.51 (m, 1 H), 1.42–1.23 (m, 3 H), 1.10–0.98 (m, 1 H), 0.88 (d, J = 6.5 Hz, 3 H, C*H*$_3$CH), 0.87 (s, 9 H, SiC(CH$_3$)$_3$), 0.05 (s, 3 H, Si(CH$_3$)$_2$), −0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.4, 152.9, 142.2, 131.2, 125.8, 118.7, 114.8, 78.6, 67.9, 35.5, 34.6, 32.7, 27.5, 26.9, 25.8, 25.7, 18.9, 16.5, 13.7, −4.8, −5.1; FAB HRMS (NBA/NaI) *m/e* 446.2534, M + Na$^+$ calcd for $C_{23}H_{41}NO_2SSi$ 446.2525.

Aldehyde 7. Oxidation of Alcohol 35. Alcohol **35** (1.9 g, 4.5 mmol) was dissolved in CH_2Cl_2 (45 mL, 0.1 M). DMSO (13.5 mL), Et_3N (3.0 mL, 22.4 mmol, 5.0 equiv), and SO_3·pyr (1.43 g, 8.98 mmol, 2.0 equiv) were added at 25 °C, and the resulting mixture was stirred for 30 min. Saturated aqueous NH_4Cl solution (100 mL) and ether (200 mL) were added sequentially. The organic phase was washed with brine (2 × 30 mL) and dried ($MgSO_4$), and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 30% ether in hexanes) furnished aldehyde **7** (1.79 g, 94%): R_f = 0.55 (silica gel, 40% ether in hexanes); $[\alpha]^{22}_D$ +13.3 (*c* 0.7, $CHCl_3$); IR (thin film) ν_{max} 2930, 2856, 1725, 1504, 1462, 1385, 1253, 1182, 1076, 938, 836, 776 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.57, (d, J = 1.8 Hz, 1 H, CHO), 6.91 (s, 1 H, SCH=C), 6.44 (s, 1 H, C*H*=CCH$_3$), 5.45–5.35 (m, 2 H, CH=CH), 4.11 (dd, J = 6.6, 6.3 Hz, 1 H, CHOSi), 2.69 (s, 3 H, N=C(S)CH$_3$), 2.34–2.24 (m, 3 H), 2.05–2.01 (m, 2 H), 1.98 (s, 3 H, CH=CC*H*$_3$), 1.71–1.64 (m, 1 H), 1.41–1.29 (m, 3 H), 1.05 (d, J = 7.0 Hz, 3 H, C*H*$_3$CH), 0.87 (s, 9 H, SiC(CH$_3$)$_3$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), −0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 205.2, 164.4, 153.0, 142.0, 130.6, 126.4, 118.8, 115.0, 78.7, 46.2, 34.7, 30.0, 27.3, 26.9, 25.8, 19.2, 18.2, 13.9, 13.2, −4.7, −5.0; FAB HRMS (NBA) *m/e* 422.2559, M + H$^+$ calcd for $C_{23}H_{39}NO_2SSi$ 422.2549.

Aldol Reaction of Keto Acid 9 with Aldehyde 7. A solution of keto acid **9** (1.52 g, 5.10 mmol, 1.2 equiv) in THF (10 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (1.78 mL, 12.78 mmol) was added to *n*-BuLi (7.95 mL, 1.6 M solution in hexanes, 12.78 mmol) in 20 mL of THF at 0 °C] at −78 °C. After being stirred for 15 min, the solution was allowed to warm to −40 °C, and after 0.5 h at that temperature, it was recooled to −78 °C. A solution of aldehyde **7** (1.79 g, 4.24 mmol, 1.0 equiv) was added dropwise, and the resulting mixture was stirred for 15 min and then quenched at −78 °C by slow addition of saturated aqueous NH_4Cl solution (20 mL). The reaction mixture was warmed to 0 °C, and AcOH (2.03 mL, 26.84 mmol, 6.3 equiv) was added, followed by addition of EtOAc (50 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic solution was dried over $MgSO_4$ and concentrated under vacuum to afford a mixture of aldol products **36a**:**36b** in a ca. 1:1 ratio (^{1}H NMR) and unreacted keto acid **9**. The mixture was dissolved in CH_2Cl_2 (50 mL) and treated, at 0 °C, with 2,6-lutidine (3.2 mL, 27.36 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.2 mL, 18.24 mmol). After stirring for 2 h (complete reaction by TLC), aqueous HCl (20 mL, 10% solution) was added and the resulting biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic solution was washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a mixture of the tetra-*tert*-butyldimethylsilyl ethers **37a,b**. The crude product was dissolved in MeOH (50 mL), and K_2CO_3 (1.40 g, 10.20 mmol) was added at 25 °C. The reaction mixture was vigorously stirred for 15 min and then filtered. The residue was washed with MeOH (20 mL), and the solution was acidified with ion-exchange resin (DOWEX 50WX8–200) to pH 4–5 and filtered again. The solvent was removed under reduced pressure, and the resulting residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous NH_4Cl solution (50 mL). The aqueous phase was extracted with EtOAc (4 × 25 mL), and the combined organic solution was dried ($MgSO_4$), filtered, and concentrated to furnish a mixture of carboxylic acids **38**, **39**, and **9**. Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave pure acids **38** (1.1 g, 31% from **7**) and **39** (1.0 g, 30% from **7**) as colorless oils. **38**: R_f = 0.61 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −8.8 (*c* 0.8, $CHCl_3$); IR (thin film) ν_{max} 2931, 2856, 1712, 1466, 1254, 1083, 836 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.94 (s, 1 H, SCH=C), 6.61 (s, 1 H, C*H*=CCH$_3$), 5.44–5.41 (m, 2 H, CH=CH), 4.40 (dd, J = 6.5, 3.2 Hz, 1 H, (CH$_3$)$_2$CC*H*OSi), 4.11 (dd, J = 6.5, 5.9 Hz, 1 H, CH$_2$C*H*OSi), 3.75 (dd, J = 6.5, 3.0 Hz, 1 H, CH(CH$_3$)C*H*OSi), 3.12 (dq, J = 7.0, 6.5 Hz, 1 H, C(O)C*H*(CH$_3$)), 2.69 (s, 3 H, N=C(CH$_3$)S), 2.48 (dd, J = 16.0, 3.2 Hz, 1 H, C*H*$_2$COOH), 2.35 (dd, J = 16.0, 6.7 Hz, 1 H, C*H*$_2$COOH), 2.39–2.28 (m, 2 H, C*H*$_2$CH=CH), 2.10–1.92 (m, 2 H, CH=CHC*H*$_2$), 1.95 (s, 3 H, CH=C(C*H*$_3$)), 1.42–1.30 (m, 5 H, C*H*(CH$_3$), 2 x CH$_2$), 1.18 (s, 3 H, C(CH$_3$)$_2$), 1.10 (s, 3 H, C(CH$_3$)$_2$), 1.06 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)), 0.90–0.85 (m, 30 H, CH(C*H*$_3$), 3 x SiC(CH$_3$)$_3$), 0.12 (s, 3 H, Si(CH$_3$)$_2$), 0.09 (s, 3 H, Si(CH$_3$)$_2$), 0.07 (s, 3 H, Si(CH$_3$)$_2$), 0.05 (s, 3 H, Si(CH$_3$)$_2$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), 0.03 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 218.1, 176.7, 164.8, 152.8, 142.6, 131.3, 125.9, 118.6, 114.7, 78.6, 77.4, 73.4, 53.5, 44.9, 40.1, 38.8, 34.6, 30.7, 28.0, 27.8, 26.2, 26.0, 25.8, 23.6, 19.1, 18.8, 18.5, 18.2, 17.4, 15.7, 13.8, −3.7, −3.8, −4.2, −4.6, −4.7, −4.9; FAB HRMS (NBA/CsI) *m/e* 970.4318, M + Cs$^+$ calcd for $C_{44}H_{83}NO_6SSi_3$ 970.4303. **39**: R_f = 0.70 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ +2.2 (*c* 3.5, $CHCl_3$); IR (thin film) ν_{max} 2929, 2856, 1713, 1470, 1386, 1254, 1082, 988, 836, 776 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H, C*H*=CCH$_3$), 5.44–5.38 (m, 1 H, CH=C*H*), 5.37–5.32 (m, 1 H, C*H*=CH), 4.55 (dd, J = 6.7, 3.7 Hz, 1 H, (CH$_3$)$_2$CC*H*OSi), 4.11 (dd, J = 6.7, 6.2 Hz, 1 H, CH$_2$C*H*OSi), 3.83 (d, J = 8.4, 1 H, CH(CH$_3$)C*H*OSi), 3.09 (dq, J = 7.0, 6.9 Hz, 1 H, C(O)C*H*(CH$_3$)), 2.73 (s, 3 H, N=C(CH$_3$)S), 2.40 (dd, J = 16.3, 3.8 Hz, 1 H, C*H*$_2$COOH), 2.35–2.22 (m, 3 H, C*H*$_2$COOH, C*H*$_2$CH=CH), 1.98–1.94 (m, 2 H, CH=CHC*H*$_2$), 1.92 (s, 3 H, CH=C(C*H*$_3$)), 1.34–1.21 (m, 5 H, C*H*(CH$_3$), 2 x CH$_2$), 1.18 (s, 3 H, C(CH$_3$)$_2$), 1.07 (s, 3 H, C(CH$_3$)$_2$), 1.05 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)), 0.89 (s, 9 H, SiC(CH$_3$)$_3$), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.85 (s, 9 H, SiC(CH$_3$)$_3$), 0.82 (d, J = 6.9 Hz, 3 H, CH(C*H*$_3$)), 0.07 (s, 6 H, 2 x Si(CH$_3$)$_2$), 0.06 (s, 3 H, Si(CH$_3$)$_2$), 0.05 (s, 3 H, Si(CH$_3$)$_2$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), 0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 217.7, 175.3, 165.4, 152.4, 143.1, 131.3, 125.9, 118.3, 114.6, 78.6, 76.7, 72.3, 53.8, 45.7, 40.1, 37.9, 34.9, 34.6, 27.7, 27.3, 26.3, 26.2, 26.0, 25.8, 22.4, 19.0, 18.6, 18.2, 18.1, 16.8, 13.9, 13.5, −3.4, −3.6, −4.3, −4.6, −4.7, −4.9; FAB HRMS (NBA/CsI) *m/e* 970.4331, M + Cs$^+$ calcd for $C_{44}H_{83}NO_6SSi_3$ 970.4303.

Hydroxy Acid 5. Selective Desilylation of Tris(silyl ether) 38. A solution of tris(silyl ether) **38** (300 mg, 0.36 mmol) in THF (7.0 mL) at 25 °C was treated with TBAF (2.2 mL, 1 M solution in THF, 2.2 mmol, 6.0 equiv). After being stirred for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous HCl (10 mL, 1 N solution). The aqueous solution was extracted with EtOAc (4 × 10 mL), and the combined organic phase was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide hydroxy acid **5** (203 mg, 78%) as a yellow oil: R_f = 0.40 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −19.2 (*c* 0.1, $CHCl_3$); IR (thin film) ν_{max} 3358, 2932, 2857, 1701, 1466, 1254, 1088, 988, 835 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.95 (s, 1 H SCH=C), 6.67 (s, 1 H, C*H*=CCH$_3$), 5.58–5.54 (m, 1 H, CH=C*H*), 5.43–5.39 (m, 1 H, C*H*=CH), 4.39 (dd, J = 6.7, 3.9 Hz, 1 H, (CH$_3$)$_2$CC*H*OSi), 4.18 (dd, J = 7.5, 5.0 Hz, 1 H, CH$_2$C*H*OH), 3.78 (dd, J = 6.9, 1.0 Hz, 1 H, CH(CH$_3$)C*H*OSi), 3.11 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)C*H*CH$_3$), 2.70 (s, 3 H, N=C(CH$_3$)S), 2.43 (dd, J = 16.2, 3.9 Hz, 1 H, C*H*$_2$COOH), 2.40–2.35 (m, 2 H, C*H*$_2$CH=CH), 2.35 (dd, J = 16.2, 6.7 Hz, 1 H, C*H*$_2$COOH), 2.15–2.10 (m, 1 H, CH=CHC*H*$_2$), 2.00 (s, 3 H, CH=C-(C*H*$_3$)), 1.99–1.95 (m, 1 H, CH=CHC*H*$_2$), 1.48–1.30 (m, 5 H, C*H*(CH$_3$), 2 x CH$_2$), 1.18 (s, 3 H, C(CH$_3$)$_2$), 1.08 (s, 3 H, C(CH$_3$)$_2$), 1.05 (d, J = 6.7 Hz, 3 H, CH(C*H*$_3$)), 0.89–0.84 (m, 21 H, CH(C*H*$_3$), SiC(C*H*$_3$)$_3$), 0.09 (s, 3 H, Si(CH$_3$)$_2$), 0.05 (s, 3 H, Si(CH$_3$)$_2$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), 0.03 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 218.9, 175.4, 166.3, 152.8, 143.5, 134.4, 125.7, 119.5, 115.9, 74.4, 54.7, 45.5, 40.9, 40.0, 34.3, 31.9, 30.6, 28.9, 28.8, 27.0, 26.8, 26.7, 24.4, 20.0, 19.6, 19.3, 19.1, 17.9, 17.1, 15.5, −2.9, −3.1, −3.3, −3.8; FAB HRMS (NBA/CsI) *m/e* 856.3459, M + Cs$^+$ calcd for $C_{38}H_{69}NO_6SSi_2$ 856.3439.

Hydroxy Acid 40. Selective Desilylation of Tris(silyl ether) 39. Carboxylic acid **39** (150 mg, 0.18 mmol) was converted to hydroxy acid **40** (107 mg, 82%) according to the procedure described above for **5**. **40**: yellow oil; R_f = 0.45 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −8.0 (*c* 0.2, $CHCl_3$); IR (thin film) ν_{max} 3225, 2943, 2860, 1719,

1690, 1461, 1384, 1296, 1250, 1190, 1085, 985, 832, 761, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.93 (s, 1 H SCH=C), 6.60 (s, 1 H, C*H*=CCH$_3$), 5.54–5.50 (m, 1 H, CH=C*H*), 5.40–5.34 (m, 1 H, C*H*=CH), 4.54 (dd, J = 6.4, 3.7 Hz, 1 H, (CH$_3$)$_2$CC*H*OSi), 4.15 (dd, J = 6.5, 6.3 Hz, 1 H, CH$_2$C*H*OH), 3.82 (d, J = 7.6 Hz, 1 H, CH(CH$_3$)C*H*OSi), 3.09 (dq, J = 6.9, 6.5 Hz, 1 H, C(O)C*H*CH$_3$), 2.71 (s, 3 H, N=C(CH$_3$)S), 2.37–2.32 (m, 3 H, C*H*$_2$CH=CH, C*H*$_2$COOH), 2.30 (dd, J = 16.3, 6.4 Hz, 1 H, C*H*$_2$COOH), 2.15–2.10 (m, 2 H, CH=CHC*H*$_2$), 1.97 (s, 3 H, CH=C(C*H*$_3$)), 1.36–1.18 (m, 5 H, C*H*(CH$_3$), 2 x CH$_2$), 1.17 (s, 3 H, C(CH$_3$)$_2$), 1.07 (s, 3 H, C(CH$_3$)$_2$), 1.05 (d, J = 6.8 Hz, 3 H, CH(C*H*$_3$)), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.85–0.82 (m, 12 H, CH(C*H*$_3$), SiC(CH$_3$)$_3$), 0.07 (s, 3 H, Si(CH$_3$)$_2$), 0.06 (s, 3 H, Si(CH$_3$)$_2$), 0.05 (s, 6 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 218.2, 175.4, 165.4, 152.2, 142.0, 133.1, 124.9, 118.6, 115.1, 74.4, 53.8, 45.8, 40.2, 38.9, 37.7, 34.8, 33.2, 27.9, 27.5, 27.1, 26.2, 26.1, 26.0, 22.6, 21.4, 18.8, 18.6, 16.9, 14.5, 13.3, −3.4, −3.6, −4.3, −4.6; FAB HRMS (NBA/CsI) *m/e* 856.3402, M + Cs$^+$ calcd for $C_{38}H_{69}NO_6SSi_2$ 856.3439.

Lactone 41. Macrolactonization of Hydroxy Acid 5. A solution of hydroxy acid **5** (200 mg, 0.28 mmol) in THF (4 mL) was treated at 0 °C with Et$_3$N (0.23 mL, 1.68 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (0.22 mL, 1.40 mmol, 5.0 equiv). The reaction mixture was stirred at 0 °C for 15 min and then added to a solution of 4-DMAP (342 mg, 2.80 mmol, 10.0 equiv) in toluene (140 mL) at 25 °C and stirred at that temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to a small volume and filtered through silica gel. The residue was washed with 40% ether in hexanes, and the resulting solution was concentrated. Purification by flash column chromatography (silica gel, 2% MeOH in CH_2Cl_2) furnished lactone **41** (178 mg, 90%) as a colorless oil: R_f = 0.37 (silica gel, 30% ether in hexanes); $[\alpha]^{22}_D$ −22.9 (*c* 0.3, $CHCl_3$); IR (thin film) ν_{max} 2925, 2854, 1734, 1693, 1464, 1381, 1252, 1187, 1158, 1099, 988, 829, 758 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.98 (s, 1 H, SCH=C), 6.58 (s, 1 H, C*H*=CCH$_3$), 5.53 (m, 1 H, CH=C*H*), 5.43–5.34 (m, 1 H, C*H*=CH), 5.00 (d, J = 10.2 Hz, 1 H, O=COCH), 4.03 (d, J = 10.5 Hz, 1 H, CHOSi), 3.89 (d, J = 9.0 Hz, 1 H, CHOSi), 2.98 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)C*H*CH$_3$), 2.85 (d, J = 16.7 Hz, 1 H, CH$_2$COO), 2.72 (s, 3 H, N=C(CH$_3$)S), 2.66 (dd, J = 16.7, 10.7 Hz, 1 H, CH$_2$COO), 2.40–2.30 (m, 1 H, CH=CHC*H*$_2$), 2.11 (s, 3 H, CH=C(C*H*$_3$)), 2.10–2.04 (m, 2 H, C*H*$_2$CH=CH), 1.92–1.83 (m, 1 H, CH=CHC*H*$_2$), 1.66–1.38 (m, 5 H, C*H*(CH$_3$), 2 x CH$_2$), 1.17 (s, 3 H, C(CH$_3$)$_2$), 1.13 (s, 3 H, C(CH$_3$)$_2$), 1.06 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)), 0.94 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)), 0.92 (s, 9 H, SiC(CH$_3$)$_3$), 0.83 (s, 9 H, SiC(CH$_3$)$_3$), 0.09 (s, 3 H, Si(CH$_3$)$_2$), 0.07 (s, 3 H, Si(CH$_3$)$_2$), 0.05 (s, 3 H, Si(CH$_3$)$_2$), −0.12 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 215.0, 171.3, 165.4, 135.7, 135.1, 125.8, 122.7, 119.9, 115.9, 79.5, 76.4, 53.3, 48.0, 38.8, 31.7, 31.3, 29.7, 29.2, 28.4, 26.4, 26.2, 26.1, 25.9, 24.2, 19.1, 18.7, 18.6, 17.7, 15.3, −3.1, −3.2, −3.7, −5.8; FAB HRMS (NBA) *m/e* 706.4382, M + H$^+$ calcd for $C_{38}H_{67}NO_5SSi_2$ 706.4357.

Lactone 42. Macrolactonization of Hydroxy Acid 40. The cyclization of hydroxy acid **40** (100 mg, 0.14 mmol) was carried out exactly as described for **41** above and yielded lactone **42** (84 mg, 85%) as a colorless oil: R_f = 0.40 (silica gel, 30% ether in hexanes); $[\alpha]^{22}_D$ −40.5 (*c* 0.2, $CHCl_3$); IR (thin film) ν_{max} 2929, 2855, 1739, 1690, 1469, 1384, 1253, 1180, 1089, 1053, 985, 835, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.94 (s, 1 H, SCH=C), 6.53 (s, 1 H, C*H*=CCH$_3$), 5.55–5.46 (m, 1 H, CH=C*H*), 5.39–5.30 (m, 1 H, C*H*=CH), 5.32 (dd, J = 7.0, 3.0 Hz, 1 H, O=COCH), 4.43 (dd, J = 7.5, 2.9 Hz, 1 H, CHOSi), 3.99 (d, J = 7.1 Hz, 1 H, CHOSi), 3.20 (dq, J = 7.3, 7.1 Hz, 1 H, C(O)C*H*CH$_3$), 2.71 (s, 3 H, N=C(CH$_3$)S), 2.59 (m, 1 H, CH=CHC*H*$_2$), 2.21 (dd, J = 14.6, 3.2 Hz, 1 H, CH$_2$COO), 2.20 (dd, J = 14.6, 7.6 Hz, 1 H, CH$_2$COO), 2.16 (s, 3 H, CH=C(C*H*$_3$)), 2.15–1.95 (m, 3 H, CH=CHC*H*$_2$, C*H*$_2$CH=CH), 1.60–1.50 (m, 3 H, C*H*(CH$_3$), 2 x CH$_2$), 1.47–1.35 (m, 2 H, C*H*(CH$_3$), 2 x CH$_2$), 1.24 (s, 3 H, C(CH$_3$)$_2$), 1.11 (d, J = 7.2 Hz, 3 H, CH(C*H*$_3$)), 1.09 (s, 3 H, C(CH$_3$)$_2$), 0.90 (s, 9 H, SiC(CH$_3$)$_3$), 0.86 (s, 9 H, SiC(CH$_3$)$_3$), 0.83 (d, J = 6.7 Hz, 3 H, CH(C*H*$_3$)), 0.09 (s, 6 H, 2 x Si(CH$_3$)$_2$), 0.01 (s, 3 H, Si(CH$_3$)$_2$), −0.05 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 221.2, 171.6, 165.8, 134.9, 134.1, 125.7, 125.2, 120.7, 117.1, 78.8, 75.2, 74.5, 54.3, 48.1, 42.5, 37.9, 33.7, 32.4, 26.8, 26.7, 26.5, 26.2, 25.8, 19.7, 19.2, 19.0, 18.8, 17.7, 15.9, 14.1, −3.0, −3.3, −3.7, −4.3; FAB HRMS (NBA) *m/e* 706.4333, M + H$^+$ calcd for $C_{38}H_{67}NO_5SSi_2$ 706.4357.

Dihydroxy Lactone 3. To lactone **41** (50 mg, 0.071 mmol), cooled to −20 °C, was added a freshly prepared 20% (v/v) CF_3COOH solution in CH_2Cl_2 (400 μL). The reaction mixture was allowed to reach 0 °C and was stirred for 1 h at that temperature. The solvents were evaporated under reduced pressure, and the crude product was purified by preparative thin-layer chromatography (silica gel, 6% MeOH in CH_2Cl_2) to afford pure dihydroxy lactone **3** (31 mg, 92%): R_f = 0.38 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −80.2 (*c* 1.7, $CHCl_3$); IR (thin film) ν_{max} 3470, 2929, 1733, 1686, 1464, 1380, 1250, 1182, 1045, 978, 732 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.83 (s, 1 H, SCH=C), 6.56 (s, 1 H, C*H*=CCH$_3$), 5.48 (dd, J = 7.0, 3.0 Hz, 1 H, O=COCH), 5.43–5.41 (m, 2 H, CH=CH), 4.21 (d, J = 11.5 Hz, 1 H, C*H*OH), 3.77 (bs, 1 H, C*H*OH), 3.13 (bs, 1 H, OH), 3.01 (bs, 1 H, OH), 2.95 (m, 1 H, C(O)C*H*CH$_3$), 2.70–2.62 (m, 1 H, CH$_2$COO), 2.47 (ddd, J = 14.6, 11.5 Hz, 1 H, CH$_2$COO), 2.27 (s, 3 H, N=C(CH$_3$)S), 2.18–2.12 (m, 2 H, CH=CHC*H*$_2$), 2.15 (s, 3 H, CH=C(C*H*$_3$)), 1.97–1.83 (m, 2H, C*H*$_2$CH=CH), 1.56–1.50 (m, 1 H, C*H*(CH$_3$)), 1.41–1.22 (m, 4 H, 2 x CH$_2$), 1.15 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)), 1.07 (d, J = 6.0 Hz, 3 H, CH(C*H*$_3$)), 1.07 (s, 3 H, C(CH$_3$)$_2$), 1.06 (s, 3 H, C(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, C_6D_6) δ 220.2, 170.6, 165.4, 153.8, 139.2, 134.1, 126.1, 120.4, 116.9, 79.2, 74.9, 73.2, 54.2, 42.5, 40.3, 39.5, 32.9, 32.6, 28.6, 28.4, 23.3, 19.3, 19.1, 16.4, 16.3, 14.4; FAB HRMS (NBA/CsI) *m/e* 610.1580, M + Cs$^+$ calcd for $C_{26}H_{39}NO_5S$ 610.1603.

Dihydroxy Lactone 43. Lactone **42** (38.0 mg, 0.054 mmol) was treated with CF_3COOH in exactly the same way as described above for **3**, yielding dihydroxy lactone **43** (24.5 mg, 95%): R_f = 0.30 (silica gel, 6% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −93.1 (*c* 0.1, $CHCl_3$); IR (thin film) ν_{max} 3450, 2929, 1735, 1685, 1464, 1380, 1250, 1182, 1045, 978, 732 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.96 (s, 1 H, SCH=C), 6.51 (s, 1 H, C*H*=CCH$_3$), 5.60–5.50 (m, 2 H, CH=CH), 5.40–5.32 (m, 1 H, O=COCH), 4.25 (d, J = 9.5 Hz, 1 H, C*H*OH), 3.55 (d, J = 9.6 Hz, 1 H, C*H*OH), 3.39 (bs, 1 H, OH), 3.31 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)C*H*CH$_3$), 2.99 (bs, 1 H, OH), 2.71 (s, 3 H, N=C(CH$_3$)S), 2.69–2.61 (m, 1 H, CH=CHC*H*$_2$), 2.59 (d, J = 16.3 Hz, 1 H, CH$_2$COO), 2.45–2.35 (m, 2 H, CH$_2$COO, CH=CHC*H*$_2$), 2.20–2.10 (m, 1 H, C*H*$_2$CH=CH), 2.08 (s, 3 H, CH=C(C*H*$_3$)), 1.98–1.90 (m, 1 H, C*H*$_2$CH=CH), 1.59–1.50 (m, 1 H, C*H*(CH$_3$)), 1.49–1.30 (m, 4 H, 2 x CH$_2$), 1.17 (s, 3 H, C(CH$_3$)$_2$), 1.11 (d, J = 6.9 Hz, 3 H, CH(C*H*$_3$)), 1.03 (s, 3 H, C(CH$_3$)$_2$), 1.01 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 222.2, 171.1, 165.2, 153.5, 139.5, 133.2, 125.1, 120.0, 116.7, 78.4, 74.1, 72.9, 52.5, 40.7, 39.5, 37.9, 34.5, 32.7, 31.3, 27.6, 24.7, 22.2, 18.9, 17.5, 15.5, 15.3; FAB HRMS (NBA) *m/e* 478.2610, M + H$^+$ calcd for $C_{26}H_{39}NO_5S$ 478.2627.

Epothilone A (1). Epoxidation of Lactone 3 with Methyl(trifluoromethyl)dioxirane. To a solution of **3** (10 mg, 21.0 μmol) in MeCN (200 μL) was added 4 × 10^{-4} M aqueous solution of disodium ethylenediaminetetraacetate (Na$_2$EDTA, 120 μL), and the reaction mixture was cooled to 0 °C. 1,1,1-Trifluoroacetone (200 μL) was added followed by a mixture of Oxone (61 mg, 0.10 mmol, 5.0 equiv) and $NaHCO_3$ (14.0 mg, 0.17 mmol, 8.0 equiv) with stirring until completion of the reaction was revealed by TLC. The reaction mixture was treated with excess Me$_2$S (100 μL) and water (500 μL) and was then extracted with EtOAc (4 × 2 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated. Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave a mixture of epothilones A (**1**) and its α-epoxide epimer (8.6 mg, 78% total yield). A second preparative thin-layer chromatography (silica gel, 70% EtOAc in hexanes) furnished pure epothilone A (**1**) (6.4 mg, 65%) as a white solid. For a more extensive study of the epoxidation of **3** and isolation of a number of epothilone A analogues, see ref 29. **1**: R_f = 0.23 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −45.0 (*c* 0.02, MeOH); IR (thin film) ν_{max} 3476, 2974, 1738, 1692 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 6.71 (s, 1 H, C*H*=CCH$_3$), 6.45 (s, 1 H, SCH=C), 5.45 (dd, J = 8.2, 2.3 Hz, 1 H, O=COCH), 4.15 (dd, J = 10.8, 2.9 Hz, 1 H, C*H*OH), 3.81–3.78 (m, 1 H, C*H*OH), 3.65 (bs, 1 H, OH), 3.03 (dq, J = 6.9, 6.5 Hz, 1 H, C(O)C*H*CH$_3$), 2.77 (ddd, J = 7.9, 4.0, 4.0 Hz, 1 H, CH$_2$C*H*O), 2.62–2.58 (m, 1 H, CH$_2$C*H*O), 2.40 (dd, J = 14.4, 10.8 Hz, 1 H, CH$_2$COO), 2.26 (bs, 1 H, OH), 2.21 (s, 3 H, N=C(CH$_3$)S), 2.19 (dd, J = 14.4, 2.9 Hz, 1 H, CH$_2$COO), 2.05 (s, 3 H, CH=C(C*H*$_3$)), 1.86 (ddd, J = 15.2, 2.5, 2.5 Hz, 1 H, C*H*$_2$CHO), 1.81–1.74

(m, 1 H, CH_2CHO), 1.68 (ddd, J = 15.2, 7.6, 7.6 Hz, 1 H, CH_2CHO), 1.53−1.49 (m, 1 H, CH_2CHO), 1.40−1.15 (m, 5 H, $CH(CH_3)$, 2 x CH_2), 1.06 (d, J = 7.0 Hz, 3 H, $CH(CH_3)$), 1.03 (s, 3 H, $C(CH_3)_2$), 0.97 (s, 3 H, $C(CH_3)_2$), 0.95 (d, J = 6.9 Hz, 3 H, $CH(CH_3)$); ^{13}C NMR (150.9 MHz, C_6D_6) δ 219.0, 170.2, 164.7, 153.0, 137.5, 119.9, 116.6, 76.6, 75.2, 73.5, 57.2, 54.2, 52.9, 43.8, 39.1, 36.3, 31.7, 30.3, 27.3, 23.9, 21.1, 20.6, 18.7, 17.4, 15.7, 14.6; HRMS (FAB), calcd for $C_{26}H_{39}CsNO_6S$ ($M + Cs^+$) 626.1552, found 626.1531.

6*S*,7*R*-Epothilones 44 and 45. Epoxidation of Lactone 43. To a solution of lactone **43** (9.0 mg, 18.8 μmol) in MeCN (0.5 mL) were added disodium ethylenediaminetetraacetate (Na_2EDTA, 4 × 10^{-4} M aqueous solution, 200 μL) and 1,1,1-trifluoroacetone (200 μL) at 0 °C. The resulting solution was stirred at 0 °C, while a mixture of solid Oxone (58 mg, 94.0 mmol, 5.0 equiv) and $NaHCO_3$ (14.0 mg, 0.17 mmol, 8.8 equiv) was added portionwise until completion of the reaction was established by TLC). The reaction mixture was treated with excess Me_2S (100 μL) and water (500 μL) and was extracted with EtOAc (4 × 2 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated. Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave a mixture of epothilones **44** and **45** (8.1 mg, 87% total yield, ca. 2:1 ratio by ^1H NMR). The major diastereoisomer (**44**, stereochemistry unassigned) was isolated by preparative thin-layer chromatography (silica gel, 70% EtOAc in hexanes) (5.4 mg, 58%) and exhibited the following properties: R_f = 0.23 (silica gel, 6% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −20.0 (*c* 0.2, $CHCl_3$); IR (thin film) ν_{max} 3448, 2919, 1725, 1684, 1455, 1378, 1284, 1149, 1061, 1020, 973, 750 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 6.99 (s, 1 H, SCH=C), 6.68 (s, 1 H, CH=CCH_3), 5.64−5.61 (m, 1 H, O=COCH), 4.43 (d, J = 2.1 Hz, 1 H, OH), 4.29 (ddd, J = 7.6, 2.5, 2.5 Hz, 1 H, CHOH), 3.82 (d, J = 8.2 Hz, 1 H, CHOH), 3.35 (bs, 1 H, OH), 3.22 (q, J = 7.0 Hz, 1 H, C(O)$CH$$CH_3$), 3.14 (ddd, J = 10.3, 4.1, 3.2 Hz, 1 H, CH_2CHO), 2.90 (ddd, J = 10.3, 4.3, 2.3 Hz, 1 H, CH_2CHO), 2.71 (s, 3 H, N=$C(CH_3)$S), 2.54 (dd, J = 13.7, 7.6 Hz, 1 H, CH_2COO), 2.51 (dd, J = 13.7, 2.5 Hz, 1 H, CH_2COO), 2.21−2.19 (m, 1 H, CH_2-CHO), 2.18 (s, 3 H, CH=$C(CH_3)$), 1.94 (ddd, J = 15.3, 10.3, 3.7 Hz, 1 H, CH_2CHO), 1.77−1.69 (m, 2 H, CH_2CHO), 1.60−1.00 (m, 5 H, $CH(CH_3)$, 2 x CH_2), 1.15 (s, 3 H, $C(CH_3)_2$), 1.14 (d, J = 6.9 Hz, 3 H, $CH(CH_3)$), 1.06 (s, 3 H, $C(CH_3)_2$), 1.02 (d, J = 7.0 Hz, 3 H, CH-(CH_3)); ^{13}C NMR (150.9 MHz, $CHCl_3$) δ 221.8, 172.1, 165.1, 152.6, 134.7, 119.8, 116.8, 76.0, 74.4, 72.8, 56.4, 53.8, 53.0, 40.2, 39.1, 34.1, 32.7, 29.4, 27.8, 22.7, 20.9, 19.0, 16.1, 15.9, 15.0, 11.8; FAB HRMS (NBA) *m/e* 494.2587, $M + H^+$ calcd for $C_{26}H_{39}NO_6S$ 494.2576.

Olefinic Compound 48. Phosphonium salt **12** (9.0 g, 12.93 mmol, 1.5 equiv) was dissolved in THF (90 mL), and the solution was cooled to 0 °C. Sodium bis(trimethylsilyl)amide (NaHMDS, 1.0 M solution in THF, 12.84 mL, 12.84 mmol, 1.48 equiv) was slowly added, and the resulting mixture was stirred at 0 °C for 15 min. The reaction mixture was then cooled to −20 °C before ketone **11** (2.23 g, 8.62 mmol, 1.0 equiv) in THF (10 mL) was added, and the reaction mixture was stirred at the same temperature for 12 h. Saturated aqueous NH_4Cl solution (50 mL) was added, and the mixture was extracted with ether (200 mL). The organic phase was washed with brine (2 × 100 mL), dried ($MgSO_4$), and concentrated to afford, after flash column chromatography (silica gel, 2% ether in hexanes), olefins **48** (3.8 g, 73%, *Z*:*E* ca. 1:1 by ^1H NMR).

Hydroxy Olefins 49. Desilylation of Silyl Ether 48. Silyl ether **48** (3.80 g, 6.88 mmol) was dissolved in CH_2Cl_2:MeOH (1:1, 70 mL), and the solution was cooled to 0 °C prior to addition of CSA (1.68 g, 7.23 mmol, 1.05 equiv) during a 5 min period. The resulting mixture was stirred for 30 min at 0 °C and then for 1 h at 25 °C. Et_3N (1.57 mL, 7.23 mmol, 1.05 equiv) was added, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 50% ether in hexanes) furnished pure hydroxy compound **49** (2.9 g, 97%).

Aldehyde 8′. Oxidation of Alcohol 49. Alcohol **49** (mixtures of *Z* and *E* geometrical isomers, 4.60 g, 10.64 mmol) was dissolved in CH_2Cl_2 (105 mL, 0.1 M). DMSO (35 mL), Et_3N (7.4 mL, 53.20 mmol, 5.0 equiv), and SO_3·pyr (3.4 g, 21.28 mmol, 2.0 equiv) were added at 25 °C, and the resulting mixture was stirred for 30 min. Saturated aqueous NH_4Cl solution (50 mL) and ether (300 mL) were added, and the organic phase was separated and washed with brine (2 × 30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash column chromatography (silica gel, 20% ether in hexanes) furnished aldehyde **8′** (4.40 g, mixture of *Z*:*E* isomers, ca. 1:1, 95%).

Tris(silyl ethers) 52′ and 53′. Aldol Reaction of Keto Acid 9 with Aldehyde 8′. A solution of keto acid **9** (773 mg, 2.56 mmol, 1.2 equiv) in THF (7.0 mL) was reacted with aldehyde **8′** (930 mg, mixture of *Z*:*E* olefins, ca. 1:1; 2.13 mmol, 1.0 equiv) according to the same procedure as described above for the condensation of **9** and **7**, to afford, after similar processing, pure carboxylic acids **52′** (564 mg, mixture of *Z* and *E* isomers, ca. 1:1, 31% from **8′**) and **53′** (545 mg, mixture of *Z* and *E* isomers, ca. 1:1, 30% from **8′**) as colorless oils and recovered keto acid **9** (125 mg).

Hydroxy Acid 6′. Selective Desilylation of 52′. Carboxylic acid **52′** (300 mg, mixture of *Z* and *E* isomers, ca. 1:1, 0.35 mmol) was converted to hydroxy acid **6′** (194 mg, mixture of *Z* and *E* isomers, ca. 1:1, 75%) according to the same procedure described above for hydroxy acid **5**.

Lactones 54 and 55. Macrolactonization of Hydroxy Acid 6′. A solution of hydroxy acid **6′** (140 mg, mixture of *Z* and *E* isomers, ca. 1:1, 0.189 mmol) in THF (2.6 mL) was treated at 0 °C with Et_3N (58 μL, 0.416 mmol, 2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (29.4 μL, 0.246 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 1 h and then added to a solution of 4-DMAP (233 mg, 1.896 mmol, 10.0 equiv) in toluene (90 mL, 0.002 M) at 25 °C and stirred at that temperature for 10 h. The solvents were removed in vacuo, and the crude product obtained was suspended in 40% ether in hexanes and filtered through silica gel. Concentration followed by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave pure lactones **54** (50 mg, 37%) and **55** (54 mg, 40%) as colorless oils. **54**: R_f = 0.40 (silica gel, 1% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −11.8 (*c* 0.8, $CHCl_3$); IR (thin film) ν_{max} 2931, 2848, 1737, 1690, 1461, 1378, 1249, 1184, 1158, 1097, 1020, 984, 835, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.95 (s, 1 H, SCH=C), 6.56 (s, 1 H, CH=CCH_3), 5.16 (dd, J = 8.4, 7.5 Hz, 1 H, CH_3C=$CHCH_2$), 4.96 (d, J = 10.1 Hz, 1 H, CH_2COOCH), 4.02 (d, J = 9.9 Hz, 1 H, CHOSi), 3.88 (d, J = 8.9 Hz, 1 H, CHOSi), 3.02 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)$CH$$CH_3$), 2.79 (d, J = 15.6 Hz, 1 H, CH_2COOCH), 2.70 (s, 3 H, N=$C(CH_3)$S), 2.70−2.65 (m, 2 H), 2.48−2.40 (m, 1 H), 2.10 (s, 3 H, CH=$C(CH_3)$), 2.10−2.04 (m, 2 H), 1.75−1.69 (m, 2 H), 1.67 (s, 3 H, $CH_2C(CH_3)$=CH), 1.66−1.45 (m, 3 H), 1.18 (s, 3 H, $C(CH_3)_2$), 1.13 (s, 3 H, $C(CH_3)_2$), 1.09 (d, J = 6.8 Hz, 3 H, $CH(CH_3)$), 0.97 (d, J = 6.8 Hz, 3 H, CH-(CH_3)), 0.94 (s, 9 H, $SiC(CH_3)_3$), 0.84 (s, 9 H, $SiC(CH_3)_3$), 0.10 (s, 3 H, $Si(CH_3)_2$), 0.09 (s, 3 H, $Si(CH_3)_2$), 0.07 (s, 3 H, $Si(CH_3)_2$), −0.12 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 215.1, 171.2, 164.6, 152.5, 140.6, 138.8, 119.3, 119.1, 115.9, 79.9, 76.3, 53.4, 39.1, 32.4, 31.9, 31.4, 29.7, 27.4, 26.4, 26.1, 26.0, 24.5, 24.3, 23.1, 19.2, 18.7, 18.6, 17.8, 15.3, −3.3, −3.7, −5.7; FAB HRMS (NBA) *m/e* 720.4534, $M + H^+$ calcd for $C_{39}H_{69}NO_5SSi_2$ 720.4513. **55**: R_f = 0.50 (silica gel, 1% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −22.7 (*c* 0.6, $CHCl_3$); IR (thin film) ν_{max} 2931, 2860, 1731, 1696, 1461, 1378, 1249, 1179, 1079, 985, 832, 773 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.92 (s, 1 H, SCH=C), 6.53 (s, 1 H, CH=CCH_3), 5.27 (dd, J = 8.0, 2.7 Hz, 1 H, CH_2COOCH), 5.16 (dd, J = 6.9, 6.6 Hz, 1 H, CH_3C=$CHCH_2$), 4.47 (t, J = 5.1 Hz, 1 H, CHOSi), 3.89 (dd, J = 4.5, 1.0 Hz, 1 H, CHOSi), 3.05 (dq, J = 6.7, 6.2 Hz, 1 H, C(O)$CH$$CH_3$), 2.70 (s, 3 H, N=$C(CH_3)$S), 2.60 (dd, J = 15.8, 5.8 Hz, 1 H, CH_2COOCH), 2.55 (m, 1 H, CH_3C=$CHCH_2$), 2.51−2.47 (m, 2 H, CH_2COOCH, CH_3C=$CHCH_2$), 2.13 (s, 3 H, CH=$C(CH_3)$), 2.10−2.05 (m, 1 H, $CH_2C(CH_3)$=CH), 1.91 (m, 1 H, $CH_2C(CH_3)$=CH), 1.68−1.45 (m, 4 H), 1.57 (s, 3 H, $CH_2C(CH_3)$=CH), 1.27−1.23 (m, 1 H), 1.17 (s, 3 H, $C(CH_3)_2$), 1.04 (d, J = 6.8 Hz, 3 H, $CH(CH_3)$), 1.07 (s, 3 H, $C(CH_3)_2$), 0.93 (d, J = 6.9 Hz, 3 H, CH-(CH_3)), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$), 0.06 (s, 3 H, $Si(CH_3)_2$), 0.05 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 217.2, 171.3, 165.5, 153.6, 139.0, 138.3, 120.9, 120.2, 117.0, 80.1, 77.2, 73.9, 54.8, 44.9, 42.7, 41.1, 40.2, 32.8, 26.9, 26.8, 25.6, 23.5, 21.1, 20.1, 19.2, 19.1, 17.7, 16.8, 16.6, 16.3, −2.7, −3.1, −3.4, −3.6; FAB HRMS (NBA) *m/e* 720.4533, $M + H^+$ calcd for $C_{39}H_{69}NO_5SSi_2$ 720.4513.

Dihydroxy Lactone 4. Dihydroxy lactone **4** was prepared from bis(silyl ether) lactone **54** (13.3 mg, 0.018 mmol) by treatment with CF_3COOH according to the same procedure described above for the preparation of **3**, to obtain pure lactone **4** (8.4 mg, 91%) as a colorless oil. **4**: R_f = 0.21 (silica gel, 4% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −91.5 (c 0.3, $CHCl_3$); IR (thin film) ν_{max} 3460, 2954, 2919, 1725, 1684, 1455, 1379, 1290, 1249, 1184, 1143, 1043, 1008, 973, 750 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.94 (s, 1 H, SCH=C), 6.57 (s, 1 H, CH=CCH_3),

5.20 (d, J = 9.7 Hz, 1 H, CH_2COOCH), 5.13 (dd, J = 9.6, 4.6 Hz, 1 H, $CH_3C{=}CHCH_2$), 4.28 (d, J = 9.7 Hz, 1 H, $(CH_3)_2CCHOH$), 3.71 (s, 1 H, $CHOH$), 3.47 (bs, 1 H, OH), 3.15 (q, J = 6.8 Hz, 1 H, C(O)-$CHCH_3$), 3.04 (bs, 1 H, OH), 2.68 (s, 3 H, N=C(CH_3)S), 2.62 (ddd, J = 15.0, 10.2, 10.1 Hz, 1 H, $CH_2CH{=}CCH_3$), 2.45 (dd, J = 14.7, 11.1 Hz, 1 H, CH_2COOCH), 2.38−2.24 (m, 1 H), 2.28 (dd, J = 14.8, 2.2 Hz, CH_2COOCH), 2.22 (d, J = 14.9 Hz, 1 H, $CH_2C(CH_3){=}CHCH_2$), 2.06 (s, 3 H, $CH{=}CCH_3$), 1.90−1.84 (m, 1 H), 1.76−1.69 (m, 1 H), 1.65 (s, 3 H, $CH_2C(CH_3){=}CH$), 1.33 (s, 3 H, $C(CH_3)_2$), 1.32−1.22 (m, 4 H), 1.19 (d, J = 6.8 Hz, 3 H, $CH(CH_3)$), 1.06 (s, 3 H, $C(CH_3)_2$), 1.00 (d, J = 7.0 Hz, 3 H, $CH(CH_3)$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 220.4, 170.2, 164.9, 151.8, 139.1, 138.3, 120.8, 119.1, 115.5, 78.9, 74.1, 72.3, 53.6, 41.7, 39.7, 32.6, 31.8, 31.7, 25.4, 23.0, 19.1, 18.1, 16.0, 15.8, 13.5; FAB HRMS (NBA) m/e 492.2795, M + H^+ calcd for $C_{27}H_{41}NO_5S$ 492.2784.

Dihydroxy Lactone 56. Dihydroxy lactone **56** was prepared from bis(silyl ether) lactone **55** (40.0 mg, 0.055 mmol) by treatment with CF_3COOH according to the same procedure described above for the preparation of **3**. Obtained pure **56** (24.3 mg, 89%): R_f = 0.19 (silica gel, 4% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −61.0 (c 0.2, $CHCl_3$); IR (thin film) ν_{max} 3418, 2932, 1731, 1691, 1466, 1381, 1252, 1159, 1067, 1044, 1012, 978, 755 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (s, 1 H, SCH=C), 6.54 (s, 1 H, $CH{=}CCH_3$), 5.38 (dd, J = 6.7, 3.8 Hz, 1 H, CH_2COOCH), 5.08 (t, J = 6.9 Hz, 1 H, $CH_3C{=}CHCH_2$), 4.32 (dd, J = 10.0, 2.4 Hz, 1 H, $(CH_3)_2CCHOH$), 3.65 (t, J = 3.4 Hz, 1 H, $CHOH$), 3.25 (dq, J = 6.7, 3.9 Hz, 1 H, C(O)$CHCH_3$), 2.68 (s, 3 H, N=C(CH_3)S), 2.55−2.43 (m, 3 H, CH_2COOCH, $C(CH_3){=}CHCH_2$), 2.40 (dd, J = 15.3, 2.5 Hz, 1 H, CH_2COOCH), 2.17−2.10 (m, 1 H, $CH_2C(CH_3){=}CH$), 2.05 (s, 3 H, $CH{=}CCH_3$), 1.95 (ddd, J = 13.4, 10.0, 3.3 Hz, 1 H, $CH_2C(CH_3){=}CH$), 1.70−1.57 (m, 3 H), 1.57 (s, 3 H, $CH_2C(CH_3){=}CH$), 1.50−1.35 (m, 2 H), 1.33 (s, 3 H, $C(CH_3)_2$), 1.15 (d, J = 6.8 Hz, 3 H, $CH(CH_3)$), 1.03 (s, 3 H, $C(CH_3)_2$), 0.97 (d, J = 7.0 Hz, 3 H, $CH(CH_3)$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 220.7, 170.7, 165.3, 152.3, 138.5, 137.4, 119.6, 119.4, 115.7, 77.7, 76.2, 71.6, 52.7, 42.7, 39.4, 39.0, 37.3, 30.7, 24.5, 20.5, 19.7, 18.7, 15.9, 15.8, 15.5, 14.3; FAB HRMS (NBA) m/e 492.2772, M + H^+ calcd for $C_{27}H_{41}NO_5S$ 492.2784.

Epothilone B (2) and Its α-Epoxide Epimer 57. Epoxidation of Lactone 4. Procedure A: To a solution of lactone **4** (3.0 mg, 6.1 μmol) in benzene (0.2 mL) at −10 °C was added m-chloroperbenzoic acid (2.9 mg, 50−60% purity, 8.4−10.1 μmol, 1.4−1.6 equiv), and the reaction mixture was stirred at that temperature for 2 h, at which time TLC indicated completion of the reaction. The reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 mL), and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) provided a mixture of epothilone B (**2**) and its α-epoxy diastereoisomer **57** (2.0 mg, 66%, ca. 5:1 ratio by ^{1}H NMR), which was separated to its components by a second preparative thin-layer chromatography (silica gel, 70% EtOAc in hexanes) furnishing pure epothilone B (**2**) (1.6 mg, 52%) as a white solid. **Procedure B:** To a solution of lactone **4** (5.0 mg, 10.2 μmol) in CH_2Cl_2 (0.5 mL) at −50 °C was added dropwise a solution of dimethyldioxirane in acetone untill the starting material disappeared (TLC). The resulting solution was concentrated, and the crude product was subjected to preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) to give epothilone B (**2**) and its α-epoxy diastereoisomer **57** in ca. 5:1 ratio (3.9 mg, 75%). Pure epothilone B (**2**) was obtained (3.1 mg, 60%) by preparative thin-layer chromatography as described above. **Procedure C:** Lactone **4** (3.0 mg, 6.1 μmol) was epoxidized with methyl(trifluoromethyl)dioxirane according to the procedure described above for the epoxidation of **3**, to yield a mixture of **2** and its α-epoxy diastereoisomer **57** in ca. 5:1 ratio by ^{1}H NMR (2.6 mg, 85% yield). The major diastereoisomer, epothilone B (**2**), was isolated as described above (2.1 mg, 69%). **2**: colorless crystals; mp 93 °C (crystallized in CH_2Cl_2/petroleum ether); R_f = 0.24 (silica gel, 4% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −34.3 (c 0.2, MeOH); IR (thin film) ν_{max} 3436, 2954, 2931, 1731, 1684, 1455, 1373, 1290, 1249, 1184, 1143, 1043, 1049, 973, 750 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.97 (s, 1 H, SCH=C), 6.59 (s, 1 H, $CH{=}CCH_3$), 5.41 (dd, J = 7.8, 2.8 Hz, 1 H, CH_2COOCH), 4.22 (bs, 2 H, $(CH_3)_2CCHOH$, OH), 3.77 (dd, J = 4.3, 4.2 Hz, 1 H, $CHOH$), 3.30 (dq, J = 6.8, 4.1 Hz, 1 H, C(O)-$CHCH_3$), 2.80 (dd, J = 7.6, 4.7 Hz, 1 H, $CHOCCH_3$), 2.70 (s, 3 H, N=C(CH_3)S), 2.64 (bs, 1 H, OH), 2.54 (dd, J = 14.0, 10.2 Hz, 1 H, CH_2COOCH), 2.36 (d, J = 14.0, 2.9 Hz, 1 H, CH_2COOCH), 2.12 (dd, J = 4.7, 2.8 Hz, 1 H, $(CH_3)COCHCH_2CHO$), 2.08 (s, 3 H, $CH{=}CCH_3$), 1.91 (ddd, J = 15.4, 7.8, 7.6 Hz, 1 H, $(CH_3)COCHCH_2CHO$), 1.77−1.68 (m, 3 H), 1.53−1.46 (m, 2 H), 1.43−1.37 (m, 2 H), 1.36 (s, 3 H, $C(CH_3)OCHCH_2$), 1.27 (s, 3 H, $C(CH_3)_2$), 1.16 (d, J = 6.9 Hz, 3 H, $CH(CH_3)$), 1.08 (s, 3 H, $C(CH_3)_2$), 1.00 (d, J = 7.0 Hz, 3 H, $CH(CH_3)$); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.34 (s, 1 H, SCH=C), 6.49 (s, 1 H, $CH{=}CCH_3$), 5.27 (dd, J = 9.0, 2.0 Hz, 1 H, CH_2COOCH), 5.07 (d, J = 6.9 Hz, 1 H, OH), 4.45 (bs, 1 H, OH), 4.08 (m, 1 H, $(CH_3)_2CCHOH$), 3.47 (d, J = 7.4 Hz, 1 H, $CHOH$), 3.10 (dq, J = 6.8, 6.5 Hz, 1 H, C(O)$CHCH_3$), 2.81 (dd, J = 9.5, 3.3 Hz, 1 H, $CHOCCH_3$), 2.64 (s, 3 H, N=C(CH_3)S), 2.40−2.30 (m, 2 H, CH_2COOCH), 2.08 (s, 3 H, $CH{=}CCH_3$), 2.05 (ddd, J = 15.0, 2.6, 1.0 Hz, 1 H, $(CH_3)COCHCH_2CHO$), 1.83 (ddd, J = 15.0, 9.3, 9.1 Hz, 1 H, $(CH_3)COCHCH_2CHO$), 1.61 (m, 1 H), 1.45−1.35 (m, 3 H), 1.35−1.25 (m, 3 H), 1.17 (s, 6 H, $C(CH_3)OCHCH_2$, $C(CH_3)_2$), 1.05 (d, J = 6.6 Hz, 3 H, $CH(CH_3)$), 0.87 (d, J = 7.0 Hz, 3 H, $CH(CH_3)$), 0.86 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR (150.9 MHz, DMSO-d_6) δ 218.1, 170.7, 164.8, 152.5, 137.6, 119.5, 118.0, 76.7, 75.7, 70.7, 61.6, 61.1, 53.3, 44.9, 35.6, 33.0, 32.1, 29.6, 23.0, 22.4, 22.0, 19.7, 18.8, 18.4, 16.4, 14.1; FAB HRMS (NBA/CsI) m/e 640.1725, M + Cs^+ calcd for $C_{27}H_{41}NO_6S$ 640.1709. A natural sample[30] of epothilone B (**2**) exhibited properties identical to those reported above.

Epothilone 58 and 59. Epoxidation of Lactone 56. Procedure A: Compound **56** (5.0 mg, 10.2 μmol) was epoxidized with mCPBA according to procedure A described above for **2** to yield a mixture of 12*S*-*epi*-epothilone B (**58**) and its α-epoxy diastereoisomer **59** (3.7 mg, 73% total yield, ca. 1:4 by ^{1}H NMR). Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave pure 12*R*-epothilone **59** (2.5 mg, 49%) as a white solid. **Procedure B:** The epoxidation of **56** (3.0 mg, 6.1 μmol) according to the procedure described above for **1** led to epothilones **58** and its α-epoxy diastereoisomer **59** (2.6 mg, 86% total yield, ca. 1:1 ratio by ^{1}H NMR). Preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) furnished pure epothilone **58** (1.3 mg, 43%) and its α-epoxy diastereoisomer **59** (1.3 mg, 43%). **58**: R_f = 0.52 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −33.1 (c 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ 6.62 (s, 1 H, $CH{=}CCH_3$), 6.44 (s, 1 H, SCH=C), 5.46 (dd, J = 7.2, 5.1 Hz, 1 H, CH_2COOCH), 4.22 (dd, J = 8.3, 3.0 Hz, 1 H, $(CH_3)_2CCHOH$), 3.71 (dd, J = 4.2, 3.6 Hz, 1 H, $CHOH$), 3.10 (dq, J = 8.6, 3.7 Hz, 1 H, C(O)$CHCH_3$), 2.95 (bs, 1 H, OH), 2.86 (dd, J = 5.8, 5.7 Hz, 1 H, $CHOCCH_3$), 2.82 (bs, 1 H, OH), 2.30 (dd, J = 14.8, 10.1 Hz, 1 H, CH_2COOCH), 2.24 (dd, J = 14.8, 3.5 Hz, 1 H, CH_2COOCH), 2.19 (s, 3 H, N=C(CH_3)S), 1.99 (s, 3 H, $CH{=}CCH_3$), 1.79−1.75 (m, 2 H), 1.74−1.70 (m, 1 H, $(CH_3)COCHCH_2CHO$), 1.60−1.55 (m, 1 H), 1.37−1.20 (m, 3 H), 1.18−1.11 (m, 1 H), 1.05 (d, J = 6.9 Hz, 3 H, $CH(CH_3)$), 1.04 (s, 6 H, $C(CH_3)OCHCH_2$), $C(CH_3)_2$), 0.92 (s, 3 H, $C(CH_3)_2$), 0.85 (d, J = 7.1 Hz, 3 H, $CH(CH_3)$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 220.3, 170.8, 134.0, 133.8, 132.3, 128.7, 116.3, 73.7, 72.2, 61.5, 59.7, 53.0, 42.5, 38.7, 38.4, 36.7, 32.4, 32.1, 22.5, 21.4, 19.5, 17.8, 15.7, 15.4, 13.9, 12.5. **59**: R_f = 0.55 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −34.5 (c 0.1, $CHCl_3$); IR (thin film) ν_{max} 3440, 2929, 1731, 1693, 1467, 1384, 1294, 1257, 1151, 1050, 977, 755 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.97 (s, 1 H, SCH=C), 6.60 (s, 1 H, $CH{=}CCH_3$), 5.50 (dd, J = 8.0, 4.0 Hz, 1 H, CH_2COOCH), 4.25 (dd, J = 10.1, 3.2 Hz, 1 H, $(CH_3)_2CCHOH$), 3.80 (bs, 1 H, OH), 3.75 (dd, J = 5.5, 3.6 Hz, 1 H, $CHOH$), 3.31 (dq, J = 6.7, 6.3 Hz, 1 H, C(O)-$CHCH_3$), 2.88 (dd, J = 6.3, 4.5 Hz, 1 H, $CHOCCH_3$), 2.69 (s, 3 H, N=C(CH_3)S), 2.59 (bs, 1 H, OH), 2.55 (dd, J = 13.5, 10.4 Hz, 1 H, CH_2COOCH), 2.45 (dd, J = 13.5, 3.7 Hz, 1 H, CH_2COOCH), 2.08 (s, 3 H, $CH{=}CCH_3$), 2.05−1.97 (m, 3 H), 1.95−1.90 (m, 1 H, $(CH_3)COCHCH_2CHO$), 1.75−1.70 (m, 2 H), 1.51−1.45 (m, 3 H), 1.37 (s, 3 H, $C(CH_3)OCHCH_2$), 1.27 (s, 3 H, $C(CH_3)_2$), 1.14 (d, J = 6.9 Hz, 3 H, $CH(CH_3)$), 1.04 (s, 3 H, $C(CH_3)_2$), 0.95 (d, J = 6.9 Hz, 3 H, $CH(CH_3)$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 219.6, 170.7, 164.9, 152.1, 136.6, 119.8, 116.4, 77.6, 75.9, 73.3, 61.3, 59.9, 52.9, 44.2, 38.8, 37.2, 36.4, 32.9, 31.3, 21.9, 21.3, 19.8, 19.4, 17.9, 17.4, 14.8; FAB HRMS (NBA/CsI) m/e 640.1686, M + Cs^+ calcd for $C_{27}H_{41}NO_6S$ 640.1709.

α,β-Unsaturated Ester 60. A mixture of aldehyde **15** (5.17 g, 15.9 mmol) and stabilized ylide **16** (8.92 g, 24.0 mmol, 1.5 equiv, prepared from 4-bromo-1-butene by (i) phosphonium salt formation, (ii) anion

formation with NaHMDS, and (iii) quenching with MeOC(O)Cl[32]) in benzene (300 mL, 0.05 M) was heated at reflux for 3 h. After being cooled to 25 °C, the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (silica gel, 30% ether in hexanes) to afford α,β-unsaturated ester **60** (7.15 g, 95%): R_f = 0.65 (silica gel, 40% ether in hexanes); $[\alpha]^{22}_D$ +10.4 (*c* 1.4, $CHCl_3$); IR (thin film) ν_{max} 2939, 2856, 1715, 1644, 1504, 1464, 1437, 1365, 1284, 1252, 1209, 1076, 955, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH=C), 6.87 (d, *J* = 7.4 Hz, 1 H, C*H*=CCOOCH$_3$), 6.47 (s, 1 H, C*H*=CCH$_3$), 5.83−5.71 (m, 1 H, C*H*=CH$_2$), 5.01−4.92 (m, 2 H, CH=C*H*$_2$), 4.19 (dd, *J* = 7.7, 4.9 Hz, 1 H, CHOSi), 3.69 (s, 3 H, COOCH$_3$), 3.05 (d, *J* = 6.0 Hz, 2 H, C*H*$_2$-CH=CH$_2$), 2.67 (s, 3 H, N=C(S)CH$_3$), 2.46 (ddd, *J* = 15.1, 7.7, 7.4 Hz, 1 H, C*H*$_2$CHOSi), 2.39 (ddd, *J* = 15.0, 7.5, 5.0 Hz, 1 H, C*H*$_2$-CHOSi), 1.99 (s, 3 H, CH=CC*H*$_3$), 0.86 (s, 9 H, SiC(CH$_3$)$_3$), 0.03 (s, 3 H, Si(CH$_3$)$_2$), −0.02 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.8, 164.4, 152.8, 141.5, 140.6, 135.3, 130.7, 119.1, 115.5, 115.1, 77.6, 51.7, 36.1, 30.9, 25.7, 19.2, 18.1, 13.9, −4.7, −5.1; FAB HRMS (NBA/CsI) *m/e* 554.1168, M + Cs^+ calcd for $C_{22}H_{35}NO_3SSi$ 554.1161.

Allylic Alcohol 61. Methyl ester **60** (6.1 g, 14.4 mmol) was dissolved in THF (80 mL) and cooled to −78 °C. DIBAL (44.0 mL, 1 M solution in CH_2Cl_2, 44.0 mmol, 3.0 equiv) was added dropwise at −78 °C, and the reaction mixture was stirred for 3 h. The reaction mixture was quenched with MeOH (1.0 mL) at −78 °C, and then ether (100 mL) was added, followed by saturated aqueous sodium−potasium tartrate solution (10 mL). The resulting mixture was allowed to warm to room temperature, where it was stirred for 3 h. The organic layer was separated, and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 40 → 80% ether in hexanes) furnished alcohol **61** (5.58 g, 98%): R_f = 0.18 (silica gel, 40% ether in hexanes); $[\alpha]^{22}_D$ +6.6 (*c* 1.1, $CHCl_3$); IR (thin film) ν_{max} 3380, 2928, 2855, 1637, 1505, 1464, 1386, 1253, 1185, 1074, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.88 (s, 1 H, SCH=C), 6.41 (s, 1 H, C*H*=CCH$_3$), 5.77−5.69 (m, 1 H, C*H*=CH$_2$), 5.48 (dd, *J* = 7.3, 7.2 Hz, 1 H, C*H*=CCH$_2$-OH), 5.00 (dd, *J* = 15.5, 3.3 Hz, 1 H, CH=C*H*$_2$), 4.93 (dd, *J* = 10.0, 3.3 Hz, 1 H, CH=C*H*$_2$), 4.12 (dd, *J* = 6.5, 6.4 Hz, 1 H, CHOSi), 3.97 (s, 2 H, C*H*$_2$OH), 2.86−2.76 (m, 2 H, C*H*$_2$CH=CH$_2$), 2.65 (s, 3 H, N=C(S)CH$_3$), 2.53 (bs, 1 H, OH), 2.36−2.24 (m, 2 H, C*H*$_2$CHOSi), 1.94 (s, 3 H, CH=CC*H*$_3$), 0.86 (s, 9 H, SiC(CH$_3$)$_3$), 0.02 (s, 3 H, Si-(CH$_3$)$_2$), −0.02 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.5, 152.8, 142.0, 138.1, 123.7, 118.7, 115.2, 114.9, 78.3, 66.6, 34.7, 32.4, 25.7, 19.0, 18.1, 13.7, −4.8, −5.0; FAB HRMS (NBA) *m/e* 394.2232, M + H^+ calcd for $C_{21}H_{35}NO_2SSi$ 394.2236.

Compound 62. Chlorination of Alcohol 61. Alcohol **61** (3.00 g, 7.60 mmol) was dissolved in CCl_4 (75 mL, 0.1 M), and Ph_3P (4.00 g, 15.2 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 100 °C for 24 h and cooled to room temperature, and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, 10% ether in hexanes) furnished pure **62** (2.6 g, 83%): R_f = 0.50 (silica gel, 15% ether in hexanes); $[\alpha]^{22}_D$ +13.7 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2953, 2928, 2855, 1637, 1504, 1470, 1439, 1387, 1254, 1182, 1075, 953, 917, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.93 (s, 1 H, SCH=C), 6.47 (s, 1 H, C*H*=CCH$_3$), 5.77−5.69 (m, 1 H, C*H*=CH$_2$), 5.66 (dd, *J* = 7.5, 7.2 Hz, 1 H, CH$_2$C*H*=CCH$_2$Cl), 5.07 (dd, *J* = 17.1, 1.6 Hz, 1 H, CH=C*H*$_2$), 5.02 (dd, *J* = 10.1, 1.4 Hz, 1 H, CH=C*H*$_2$), 4.14 (dd, *J* = 7.2, 5.5 Hz, 1 H, CHOSi), 4.02 (s, 2 H, CH$_2$Cl), 2.99−2.89 (m, 2 H, C*H*$_2$CH=CH$_2$), 2.71 (s, 3 H, N=C(S)CH$_3$), 2.52−2.27 (m, 2 H, C*H*$_2$CHOSi), 1.99 (s, 3 H, CH=CC*H*$_3$), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.05 (s, 3 H, Si(CH$_3$)$_2$), 0.00 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.3, 152.9, 141.8, 134.9, 134.7, 128.9, 119.0, 116.2, 115.2, 78.1, 49.9, 35.3, 32.3, 25.8, 19.2, 18.2, 13.9, −4.7, −5.0; FAB HRMS (NBA) *m/e* 412.1884, M + H^+ calcd for $C_{21}H_{34}$-ClNOSSi 412.1897.

Compound 63. Reduction of 62. Compound **62** (2.60 g, 6.30 mmol) was dissolved in THF (60 mL, 0.1 M) and cooled to 0 °C. $LiEt_3$-BH (12.6 mL, 1.0 M solution in THF, 12.6 mmol, 2.0 equiv) was added dropwise, and the reaction mixture was stirred at 0 °C for 1 h. Aqueous NaOH (1.0 mL, 3.0 N) solution was added followed by addition of Et_2O (150 mL). The organic phase was washed with brine (2 × 20 [illegible]. Flash column chromatography (silica gel, 20% ether in hexanes) furnished pure **63** (2.38 g, 99%): R_f = 0.60 (silica gel, 15% ether in hexanes); $[\alpha]^{22}_D$ +17.1 (*c* 0.7, $CHCl_3$); IR (thin film) ν_{max} 2928, 2856, 1637, 1505, 1464, 1253, 1181, 1075, 946, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H, C*H*=CCH$_3$), 5.77−5.68 (m, 1 H, C*H*=CH$_2$), 5.22 (dd, *J* = 7.3, 7.0 Hz, 1 H, CH$_2$C*H*=CCH$_3$), 5.01 (dd, *J* = 17.1, 3.2 Hz, 1 H, CH=C*H*$_2$), 4.96 (dd, *J* = 10.1, 3.3 Hz, 1 H, CH=C*H*$_2$), 4.09 (dd, *J* = 7.2, 5.9 Hz, 1 H, CHOSi), 2.80 (dd, *J* = 14.5, 6.5 Hz, 1 H, C*H*$_2$CH=CH$_2$), 2.73−2.68 (m, 1 H, C*H*$_2$CH=CH$_2$), 2.70 (s, 3 H, N=C(S)CH$_3$), 2.32−2.19 (m, 2 H, C*H*$_2$CHOSi), 1.99 (s, 3 H, CH=CC*H*$_3$), 1.66 (s, 3 H, CH$_2$CH=CC*H*$_3$), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), −0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.3, 153.2, 142.5, 136.0, 134.4, 122.5, 118.7, 115.1, 114.9, 78.9, 36.6, 35.3, 25.8, 23.5, 19.2, 18.2, 13.9, −4.8, −5.0; FAB HRMS (NBA) *m/e* 378.2279, M + H^+ calcd for $C_{21}H_{35}NOSSi$ 378.2287.

Primary Alcohol 64. Selective Hydroboration of Olefinic Compound 63. Compound **63** (1.1 g, 2.91 mmol) was dissolved in THF (3.0 mL, 1.0 M), and the solution was cooled to 0 °C. 9-BBN (7.0 mL, 0.5 M solution in THF, 3.5 mmol, 1.2 equiv) was added, and the reaction mixture was stirred for 2 h at 0 °C. Aqueous NaOH (7.0 mL, 3 N solution, 21.0 mmol, 7.2 equiv) was added with stirring, followed by H_2O_2 (2.4 mL, 30%, aqueous solution). Stirring was continued for 0.5 h at 0 °C, after which time the reaction mixture was diluted with ether (30 mL). The organic solution was separated, and the aqueous phase was extracted with ether (2 × 15 mL). The combined organic layer was washed with brine (2 × 5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel, 50 → 80% ether in hexanes) furnished primary alcohol **64** (1.0 g, 91%): R_f = 0.17 (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ +3.6 (*c* 0.2, $CHCl_3$); IR (thin film) ν_{max} 3381, 2953, 2929, 2856, 1723, 1660, 1469, 1444, 1376, 1253, 1185, 1073, 941, 837, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH=C), 6.44 (s, 1 H, C*H*=CCH$_3$), 5.17 (dd, *J* = 7.0, 6.9 Hz, 1 H, CH$_2$C*H*=CCH$_3$), 4.11 (dd, *J* = 7.1, 5.7 Hz, 1 H, CHOSi), 3.59 (dd, *J* = 6.5, 6.4 Hz, 2 H, C*H*$_2$OH), 2.70 (s, 3 H, N=C-(S)CH$_3$), 2.35−2.28 (m, 1 H, C*H*$_2$CHOSi), 2.27−2.20 (m, 1 H, C*H*$_2$-CHOSi), 2.10 (dd, *J* = 7.6, 7.5 Hz, 2 H C*H*$_2$CH$_2$CH$_2$OH), 1.98 (s, 3 H, CH=CC*H*$_3$), 1.67 (s, 3 H, CH$_2$CH=CC*H*$_3$), 1.67−1.58 (m, 2 H, C*H*$_2$CH$_2$OH), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), −0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.5, 153.0, 142.7, 136.2, 122.2, 118.5, 115.0, 78.9, 62.4, 35.4, 30.7, 28.0, 25.8, 23.3, 19.2, 18.3, 14.0, −4.7, −5.0; FAB HRMS (NBA) *m/e* 396.2382, M + H^+ calcd for $C_{21}H_{37}NO_2SSi$ 396.2393.

Iodide 14. Iodide **14** (1.18 g, 92%) was prepared from alcohol **64** (1.0 g, 2.53 mmol) according to the procedure described above for **27**. **14**: Colorless oil; R_f = 0.65 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ +7.5 (*c* 0.8, $CHCl_3$); IR (thin film) ν_{max} 2955, 2930, 2855, 1504, 1462, 1444, 1376, 1360, 1253, 1183, 1074, 942, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH=C), 6.46 (s, 1 H, C*H*=CCH$_3$), 5.20 (dd, *J* = 7.3, 7.1 Hz, 1 H, CH$_2$C*H*=CCH$_3$), 4.09 (dd, *J* = 7.4, 5.5 Hz, 1 H, CHOSi), 3.14 (dd, *J* = 7.1, 7.0 Hz, 2 H, CH$_2$I), 2.69 (s, 3 H, N=C(S)CH$_3$), 2.34−2.27 (m, 1 H, C*H*$_2$CHOSi), 2.26−2.19 (m, 1 H, C*H*$_2$CHOSi), 2.17−2.03 (m, 2 H), 2.00 (s, 3 H, CH=CC*H*$_3$), 1.93−1.86 (m, 2 H), 1.67 (s, 3 H, CH$_2$CH=CC*H*$_3$) 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), −0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.2, 153.1, 142.3, 134.6, 123.1, 118.6, 115.0, 78.8, 35.4, 32.6, 31.9, 25.8, 23.4, 19.2, 18.2, 14.0, 6.5, −4.7, −5.0; FAB HRMS (NBA) *m/e* 506.1422, M + H^+ calcd for $C_{21}H_{36}INOSSi$ 506.1410.

Hydrazone 65. Alkylation of SAMP Hydrazone 13 with Iodide 14. SAMP hydrazone **13**[15] (337 mg, 0.2 mmol, 2.0 equiv) in THF (2.5 mL) was added to a freshly prepared solution of LDA at 0 °C [diisopropylamine (277 μL, 0.20 mmol, 2.0 equiv) was added to *n*-BuLi (1.39 mL, 1.42 M solution in hexanes, 0.20 mmol. 2.0 equiv) in 2.5 mL of THF at 0 °C] at 0 °C. After being stirred at that temperature for 8 h, the resulting yellow solution was cooled to −100 °C and a solution of iodide **14** (0.5 g, 0.99 mmol, 1.0 equiv) in THF (3 mL) was added dropwise over a period of 5 min. The mixture was allowed to warm to −20 °C over 10 h and then poured into saturated aqueous NH_4Cl solution (5 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Purification by flash column chromatography on silica gel (20 → 40% ether in hexanes) provided hydrazone **65** (380 mg, 70%, de > 98% by

^{1}H NMR) as a yellow oil: $R_f = 0.17$ (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ −27.8 (*c* 2.6, $CHCl_3$); IR (thin film) ν_{max} 2931, 2861, 1724, 1653, 1599, 1499, 1451, 1374, 1249, 1178, 1077, 940, 834, 774, 727, 673 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH=C), 6.48 (d, J = 6.6 Hz, 1 H, CNH), 6.44 (s, 1 H, C*H*=CCH$_3$), 5.12 (dd, J = 7.1, 6.9 Hz, 1 H, CH$_2$C*H*=CCH$_3$), 4.07 (dd, J = 6.8, 6.2 Hz, 1 H, CHOSi), 3.55 (dd, J = 9.1, 3.7 Hz, 1 H, C*H*$_2$OCH$_3$), 3.41 (dd, J = 9.1, 6.9 Hz, 1 H, C*H*$_2$OCH$_3$), 3.36 (s, 3 H, CH$_2$OC*H*$_3$), 3.35−3.32 (m, 2 H, CH$_2$N), 2.70 (s, 3 H, N=C(S)CH$_3$), 2.69−2.62 (m, 1 H), 2.31−2.17 (m, 3 H), 2.04−1.84 (m, 5 H), 1.99 (s, 3 H, CH=CC*H*$_3$), 1.79−1.72 (m, 1 H), 1.64 (s, 3 H, CH$_2$CH=CC*H*$_3$) 1.41−1.22 (m, 4 H), 1.01 (d, J = 6.9 Hz, CHC*H*$_3$), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), −0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.2, 153.1, 144.3, 142.4, 136.6, 121.5, 118.5, 114.8, 78.9, 74.7, 63.4, 59.1, 50.4, 37.0, 35.3, 35.2, 31.8, 26.4, 25.7, 25.4, 23.3, 22.0, 19.1, 18.9, 18.1, 13.8, −4.8, −5.0; FAB HRMS (NBA) *m/e* 548.3728, M + H$^+$ calcd for $C_{30}H_{53}N_3O_2SSi$ 548.3706.

Nitrile 66. Monoperoxyphthalic acid magnesium salt (MMPP·6H$_2$O, 233 mg, 0.38 mmol, 2.5 equiv) was suspended in a rapidly stirred mixture of MeOH and pH 7 phosphate buffer (1:1, 3.0 mL) at 0 °C. Hydrazone **65** (83 mg, 0.15 mmol, 1.0 equiv) in MeOH (1.0 mL) was added dropwise, and the mixture was stirred at 0 °C until the reaction was complete by TLC (ca. 1 h). The resulting suspension was placed in a separating funnel along with ether (15 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The organic layer was separated, and the aqueous phase was extracted with ether (10 mL). The combined organic solution was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica gel, 50% ether in hexanes) afforded nitrile **66** (53 mg, 80%) as a colorless oil: $R_f = 0.44$ (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ +10.3 (*c* 3.2, $CHCl_3$); IR (thin film) ν_{max} 2926, 2855, 1503, 1457, 1381, 1250, 1179, 1072, 935, 833, 773, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1 H, SCH=C), 6.45 (s, 1 H, C*H*=CCH$_3$), 5.18 (dd, J = 7.0, 6.5 Hz, 1 H, CH$_2$C*H*=CCH$_3$), 4.08 (dd, J = 6.5, 6.0 Hz, 1 H, CHOSi), 2.70 (s, 3 H, N=C(S)CH$_3$), 2.60−2.53 (m, 1 H), 2.30−2.18 (m, 2 H), 2.11−1.97 (m, 2 H), 1.99 (s, 3 H, CH=CC*H*$_3$), 1.67 (s, 3 H, CH$_2$CH=CC*H*$_3$) 1.67−1.45 (m, 4 H), 1.29 (d, J = 6.9 Hz, CHC*H*$_3$), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), −0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.3, 153.0, 142.3, 135.5, 122.8, 122.4, 118.6, 114.9, 78.4, 35.3, 33.6, 31.1, 25.7, 25.4, 25.1, 23.2, 19.1, 18.1, 17.9, 13.9, −4.8, −5.1; FAB HRMS (NBA) *m/e* 433.2720, M + H$^+$ calcd for $C_{24}H_{40}N_2OSSi$ 433.2709.

Aldehyde 8. Nitrile **66** (53 mg, 0.12 mmol) was dissolved in toluene (2.0 mL) and cooled to −78 °C. DIBAL (245 μL, 1 M solution in toluene, 0.22 mmol, 2.0 equiv) was added dropwise at −78 °C, and the reaction mixture was stirred at that temperature until its completion was verified by TLC (ca. 1 h). Methanol (150 μL) and aqueous HCl (150 μL, 1 N solution) were sequentially added, and the resulting mixture was brought up to 0 °C and stirred at that temperature for 30 min. Ether (5 mL) and water (2 mL) were added, and the organic layer was separated. The aqueous phase was extracted with ether (2 × 5 mL), and the combined organic solution was washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 15% ether in hexanes) furnished pure aldehyde **8** (44 mg, 82%): $R_f = 0.48$ (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ +14.7 (*c* 1.7, $CHCl_3$); IR (thin film) ν_{max} 2915, 2859, 1721, 1500, 1455, 1381, 1251, 1183, 1070, 940, 832, 770 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, J = 1.9 Hz, 1 H, CHO), 6.92 (s, 1 H, SCH=C), 6.45 (s, 1 H, C*H*=CCH$_3$), 5.16 (dd, J = 7.1, 7.0 Hz, 1 H, CH$_2$C*H*=CCH$_3$), 4.08 (dd, J = 7.0, 5.5 Hz, 1 H, CHOSi), 2.70 (s, 3 H, N=C(S)CH$_3$), 2.36−2.18 (m, 3 H), 2.07−2.01 (m, 2H), 1.99 (s, 3 H, CH=CC*H*$_3$), 1.71−1.64 (m, 1 H), 1.66 (d, J = 1.0 Hz, 3 H, CH$_2$CH=CC*H*$_3$), 1.43−1.29 (m, 3 H), 1.08 (d, J = 7.0 Hz, 3 H, C*H*$_3$CH), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), −0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 205.0, 164.4, 153.1, 142.3, 135.9, 122.0, 118.6, 114.9, 78.8, 46.1, 35.3, 31.7, 30.2, 25.7, 25.1, 23.3, 19.1, 18.2, 13.8, 13.2, −4.8, −5.1; FAB HRMS (NBA) *m/e* 436.2717, M + H$^+$ calcd for $C_{24}H_{41}NO_2SSi$ 436.2706.

12*Z*-Carboxylic Acids 52 and 53. Aldol Reaction of Keto Acid 9 with 12*Z*-Aldehyde 8. A solution of keto acid **9** (365 mg, 1.21 mmol, 1.6 equiv) in THF (5.0 mL) was reacted with 12*Z*-aldehyde **8** (330 mg, 0.76 mmol, 1.0 equiv) according to the same procedure as described above for the condensation of **9** and **8** to afford, after similar processing, geometrically pure 12*Z*-carboxylic acids **52** (207 mg, 32%) and **53** (181 mg, 28%) and recovered **9**. **12*Z*-Carboxylic acid 52:** R_f = 0.56 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −2.9 (*c* 0.8, $CHCl_3$); IR (thin film) ν_{max} 2933, 2854, 1708, 1464, 1385, 1249, 1187, 1079, 983, 830, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1 H, SCH=C), 6.58 (s, 1 H, C*H*=CCH$_3$), 5.15 (dd, J = 7.4, 7.1 Hz, 1 H, (CH$_3$)C=C*H*CH$_2$), 4.39 (dd, J = 6.7, 3.0 Hz, 1 H, (CH$_3$)$_2$CC*H*OSi), 4.11 (dd, J = 7.3, 5.7 Hz, 1 H, CH$_2$C*H*OSi), 3.74 (dd, J = 6.1, 1.8 Hz, 1 H, CH(CH$_3$)C*H*OSi), 3.13 (dq, J = 7.0, 6.5 Hz, 1 H, C(O)C*H*(CH$_3$)), 2.70 (s, 3 H, N=C(CH$_3$)S), 2.44 (dd, J = 16.4, 3.1 Hz, 1 H, C*H*$_2$-COOH), 2.31 (dd, J = 16.4, 6.8 Hz, 1 H, C*H*$_2$COOH), 2.28−2.04 (m, 3 H, C*H*$_2$C(CH$_3$)=CH, CH$_2$C(CH$_3$)=CHC*H*$_2$), 1.94 (s, 3 H, CH=C-(C*H*$_3$)), 1.96−1.86 (m, 1 H), 1.66 (s, 3 H, CH$_2$C(C*H*$_3$)=CH), 1.47−1.31 (m, 4 H), 1.17 (s, 3 H, C(CH$_3$)$_2$), 1.12 (s, 3 H, C(CH$_3$)$_2$), 1.21−1.09 (m, 1 H), 1.08 (d, J = 6.8 Hz, 3 H, CH(C*H*$_3$)), 0.90−0.85 (m, 30 H, CH(C*H*$_3$), 3 x SiC(CH$_3$)$_3$), 0.10 (s, 3 H, Si(CH$_3$)$_2$), 0.06 (s, 3 H, Si(CH$_3$)$_2$), 0.05 (s, 3 H, Si(CH$_3$)$_2$), 0.03 (s, 3 H, Si(CH$_3$)$_2$), 0.02 (s, 3 H, Si(CH$_3$)$_2$), −0.02 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.2, 175.5, 165.0, 152.8, 143.4, 137.0, 121.6, 118.2, 114.5, 79.1, 73.1, 53.8, 44.4, 40.0, 39.2, 35.3, 32.4, 31.4, 26.2, 26.0, 25.8, 25.7, 23.5, 23.4, 18.8, 18.7, 18.4, 18.2, 16.8, 15.8, 13.9, −3.9, −4.0, −4.1, −4.6, −4.7, −5.0; FAB HRMS (NBA/CsI) *m/e* 984.4427, M + Cs$^+$ calcd for $C_{45}H_{85}NO_6SSi_3$ 984.4460. **12*Z*-Carboxylic acid 53:** R_f = 0.65 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ +6.2 (*c* 0.6, $CHCl_3$); IR (thin film) ν_{max} 2933, 2854, 1708, 1459, 1386, 1249, 1074, 988, 830, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H, C*H*=CCH$_3$), 5.12 (dd, J = 7.4, 6.9 Hz, 1 H, (CH$_3$)C=C*H*CH$_2$), 4.56 (dd, J = 6.1, 5.6 Hz, 1 H, (CH$_3$)$_2$CC*H*OSi), 4.07 (dd, J = 7.6, 5.6 Hz, 1 H, CH$_2$C*H*OSi), 3.85 (d, J = 8.4 Hz, 1 H, CH(CH$_3$)C*H*OSi), 3.10 (dq, J = 7.1, 7.0 Hz, 1 H, C(O)C*H*(CH$_3$)), 2.75 (s, 3 H, N=C-(CH$_3$)S), 2.43−2.10 (m, 4 H), 1.96−1.88 (m, 2 H), 1.91 (s, 3 H, CH=C-(C*H*$_3$)), 1.66 (s, 3 H, CH$_2$C(C*H*$_3$)=CH), 1.35−1.02 (m, 14 H, C*H*(CH$_3$), 2 x CH$_2$, C(CH$_3$)$_2$, C(CH$_3$)$_2$, CH(C*H*$_3$)), 0.92−0.80 (m, 30 H, 3 x SiC-(CH$_3$)$_3$, CH(C*H*$_3$)), 0.09−0.01 (m, 18 H, 3 x Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.1, 174.2, 165.4, 152.3, 143.7, 137.1, 121.6, 117.9, 114.4, 78.9, 72.4, 53.8, 45.8, 40.4, 38.3, 35.6, 35.3, 32.3, 26.7, 26.3, 26.2, 26.0, 25.8, 25.7, 23.9, 23.3, 18.6, 18.5, 18.4, 17.1, 13.9, 13.4, −3.4, −3.6, −4.3, −4.6, −4.7, −4.9; FAB HRMS (NBA/CsI) *m/e* 984.4430, M + Cs$^+$ calcd for $C_{45}H_{85}NO_6SSi_3$ 984.4460.

12*Z*-Hydroxy Acid 6. 12*Z*-Carboxylic acid **52** (400 mg, 0.47 mmol) was converted to 12*Z*-hydroxy acid **6** (253 mg, 73% yield) according to the same procedure described above for **5**. **6**: yellow oil; $R_f = 0.41$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −10.4 (*c* 0.4, $CHCl_3$); IR (thin film) ν_{max} 3227, 2933, 2852, 1711, 1696, 1468, 1387, 1245, 1189, 1087, 986, 834, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1 H SCH=C), 6.67 (s, 1 H, C*H*=CCH$_3$), 5.19 (dd, 1 H, J = 7.5, 7.0 Hz, CH$_3$C=C*H*CH$_2$), 4.41 (dd, J = 6.0, 3.5 Hz, 1 H, (CH$_3$)$_2$CC*H*OSi), 4.16 (dd, J = 6.6, 6.5 Hz, 1 H, CH$_2$C*H*OH), 3.78 (d, J = 6.9 Hz, 1 H, CH(CH$_3$)C*H*OSi), 3.13 (dq, J = 6.9, 6.6 Hz, 1 H, C(O)C*H*CH$_3$), 2.72 (s, 3 H, N=C(CH$_3$)S), 2.47 (dd, J = 16.2, 3.9 Hz, 1 H, C*H*$_2$COOH), 2.40−2.35 (m, 3 H, C*H*$_2$C(CH$_3$)=CH, C*H*$_2$COOH), 2.17−2.10 (m, 1 H, C(CH$_3$)=CHC*H*$_2$), 2.00 (s, 3 H, CH=C(C*H*$_3$)), 1.99−1.93 (m, 1 H, C(CH$_3$)=CHC*H*$_2$), 1.72 (s, 3 H, CH$_2$C(C*H*$_3$)=CH), 1.53−1.35 (m, 5 H), 1.19 (s, 3 H, C(CH$_3$)$_2$), 1.14 (s, 3 H, C(CH$_3$)$_2$), 1.07 (d, J = 6.7 Hz, 3 H, CH(C*H*$_3$)), 0.94−0.84 (m, 21 H, CH(C*H*$_3$), SiC(CH$_3$)$_3$), 0.11 (s, 3 H, Si(CH$_3$)$_2$), 0.07 (s, 6 H, Si(CH$_3$)$_2$), 0.05 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 217.9, 174.8, 165.1, 152.3, 142.1, 139.4, 120.2, 118.5, 115.0, 73.2, 53.8, 44.5, 40.0, 39.1, 34.1, 32.4, 31.2, 26.2, 26.1, 25.9, 23.5, 23.3, 18.9, 18.6, 18.3, 18.1, 16.8, 16.0, 14.6, −3.9, −4.1, −4.2, −4.7; FAB HRMS (NBA/CsI) *m/e* 870.3632, M + Cs$^+$ calcd for $C_{39}H_{71}NO_6SSi_2$ 870.3595.

Hydroxy Acid 67. 12*Z*-Carboxylic acid **53** (200 mg, 0.24 mmol) was converted to 12*Z*-hydroxy acid **67** (123 mg, 71% yield) according to the procedure described above for **5**. **67**: yellow oil; $R_f = 0.45$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −8.1 (*c* 0.3, $CHCl_3$); IR (thin film) ν_{max} 3227, 2933, 2862, 1711, 1691, 1463, 1382, 1250, 1189, 1082, 986, 834, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1 H SCH=C), 6.61 (s, 1 H, C*H*=CCH$_3$), 5.15 (dd, 1 H, J = 7.5, 7.0 Hz, CH$_3$C=C*H*CH$_2$), 4.55 (dd, J = 6.1, 3.5 Hz, 1 H, (CH$_3$)$_2$CC*H*OSi), 4.12 (dd, J = 8.0, 4.5 Hz, 1 H, CH$_2$C*H*OH), 3.86 (d, J = 8.2 Hz, 1 H, CH(CH$_3$)C*H*OSi), 3.12 (dq, J = 7.2, 7.0 Hz, 1 H, C(O)C*H*CH$_3$), 2.75 (s, 3 H, N=C(CH$_3$)S), 2.37−2.30 (m, 5 H, C*H*$_2$C(CH$_3$)=CH, C*H*$_2$-COOH, C(CH$_3$)=CHC*H*$_2$), 1.98 (s, 3 H, CH=C(C*H*$_3$)), 1.94−1.89 (m,

1 H), 1.72 (s, 3 H, $CH_2C(CH_3)$=CH), 1.39−1.04 (m, 14 H, $CH(CH_3)$, $CH(CH_3)$, 2 x CH_2, $C(CH_3)_2$), 0.95−0.84 (m, 21 H, $SiC(CH_3)_3$, $CH(CH_3)$), 0.09 (s, 3 H, $Si(CH_3)_2$), 0.08 (s, 3 H, $Si(CH_3)_2$), 0.07 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.6, 174.0, 165.6, 152.0, 142.4, 139.4, 120.1, 118.0, 114.7, 72.4, 53.8, 45.8, 40.4, 38.4, 35.5, 34.0, 32.1, 26.4, 26.2, 26.0, 25.9, 23.8, 23.6, 18.5, 18.4, 18.2, 17.2, 14.9, 13.2, −3.5, −3.7, −4.4, −4.8; FAB HRMS (NBA/CsI) *m/e* 870.3574, M + Cs^+ calcd for $C_{39}H_{71}NO_6SSi_2$ 870.3595.

Lactone 54. Macrolactonization of 12Z-Hydroxy Acid 6. 12Z-Hydroxy acid **6** (8.1 mg, 0.011 mmol) was cyclized according to the procedure described above for **6'** to afford lactone **54** (6.1 mg, 77%).

Lactone 68. Macrolactonization of 12Z-Hydroxy Acid 67. The macrolactonization of 12Z-hydroxy acid **67** (5.0 mg, 0.007 mmol) to lactone **68** (3.7 mg, 76%) was carried out according to the procedure described above for **6'**. **68**: colorless oil; R_f = 0.83 (silica gel, 2% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −31.8 (*c* 0.1, $CHCl_3$); IR (thin film) ν_{max} 2931, 2860, 1736, 1690, 1461, 1384, 1360, 1296, 1249, 1084, 985, 832, 773 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.98 (s, 1 H, SCH=C), 6.45 (s, 1 H, C*H*=CCH_3), 5.07−5.21 (m, 2 H, CH_3C=C*H*CH_2, CH_2-COOC*H*), 4.32 (dd, *J* = 6.8, 5.0 Hz, 1 H, CHOSi), 4.05 (d, *J* = 5.7 Hz, 1 H, CHOSi), 3.17 (dq, *J* = 7.0, 6.8 Hz, 1 H, C(O)C*H*CH_3), 2.70 (s, 3 H, N=$C(CH_3)$S), 2.57−2.52 (m, 1 H), 2.29 (dd, *J* = 14.4, 4.6 Hz, 1 H, C*H*$_2$COOCH), 2.27−2.13 (m, 1 H), 2.25 (dd, *J* = 14.5, 7.0 Hz, 1 H, CH_2COO), 2.20−2.15 (m, 1 H), 2.14 (s, 3 H, CH=$C(CH_3)$), 1.88−1.82 (m, 1 H), 1.57−1.52 (m, 2 H), 1.47−1.38 (m, 3 H), 1.30 (s, 3 H, $C(CH_3)_2$), 1.11 (d, *J* = 7.2 Hz, 3 H, $CH(CH_3)$), 1.08 (s, 3 H, $C(CH_3)_2$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.89−0.82 (bs, 12 H, $SiC(CH_3)_3$, $CH(CH_3)$), 0.11 (s, 3 H, $Si(CH_3)_2$), 0.09 (s, 3 H, $Si(CH_3)_2$), 0.06 (s, 3 H, $Si(CH_3)_2$), −0.03 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 220.2, 170.9, 164.8, 153.1, 140.0, 137.6, 120.2, 118.9, 116.3, 79.3, 74.0, 53.3, 48.0, 41.2, 39.7, 34.9, 31.4, 31.3, 26.6, 26.1, 25.9, 25.3, 23.9, 19.0, 18.5, 18.4, 18.1, 16.2, 14.9, 13.8, −3.9, −4.4, −4.6, −4.9; FAB HRMS (NBA/CsI) *m/e* 852.3451, M + Cs^+ calcd for $C_{39}H_{69}NO_5SSi_2$ 852.3489.

Ketone 69. To a solution of aldehyde **20** (1.3 g, 4.53 mol) in THF (20 mL) at −78 °C was added dropwise lithium tri-*tert*-butoxyaluminohydride (4.98 mL, 1.0 M solution in THF, 4.98 mmol, 1.1 equiv). After 5 min, the reaction mixture was brought up to 0 °C and stirred at that temperature for 15 min, before quenching with saturated aqueous solution of sodium−potasium tartrate (25 mL). The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude primary alcohol so obtained was dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C. Et_3N (2.5 mL, 15.85 mmol, 3.5 equiv), 4-DMAP (60 mg, 0.09 mmol, 0.02 equiv), and *tert*-butyldimethylsilyl chloride (2.0 g, 13.59 mmol, 3.0 equiv) were added. The reaction mixture was allowed to stir at 0 °C for 2 h, then at 25 °C for 10 h. MeOH (5 mL) was added, and the solvents were removed under reduced pressure. Ether (100 mL) was added followed by saturated aqueous NH_4Cl solution (25 mL), and the organic phase was separated. The aqueous phase was extracted with ether (2 × 50 mL), and the combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% ether in hexanes) provided pure bis(silyl ether) **69** (1.26 g, 70% yield from **20**): R_f = 0.67 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ −7.3 (*c* 1.8, $CHCl_3$); IR (thin film) ν_{max} 2941, 2856, 1701, 1466, 1388, 1252, 1095, 1024, 946, 832, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.06 (dd, *J* = 8.0, 3.0 Hz, 1 H, CHOSi), 3.65−3.56 (m, 2 H, CH_2OSi), 2.56 (dq, *J* = 18.5, 7.0 Hz, 1 H, C*H*$_2CH_3$), 2.46 (dq, *J* = 18.5, 7.0 Hz, 1 H, C*H*$_2CH_3$), 1.56−1.43 (m, 2 H, C*H*$_2CH_2OSi$), 1.11 (s, 3 H, $C(CH_3)_2$), 1.04 (s, 3 H, $C(CH_3)_2$), 0.98 (t, *J* = 7.0 Hz, 3 H, C*H*$_3CH_2$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.09 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 3 H, $Si(CH_3)_2$), 0.02 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 215.5, 73.2, 59.9, 52.9, 37.1, 31.4, 25.9, 25.7, 22.0, 19.8, 18.2, 18.1, 7.6, −4.1, −4.2, −5.4, −5.5; FAB HRMS (NBA) *m/e* 403.3075, M + H^+ calcd for $C_{21}H_{46}O_3Si_2$ 403.3064.

Tris(silyl ethers) 70 and 71. Aldol Reaction of Ketone 69 with Aldehyde 8. A solution of ketone **68** (270 mg, 0.67 mmol, 1.2 equiv) in THF (1.5 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (94 μL, 0.67 mmol) was added to *n*-BuLi (0.43 mL, 1.6 M solution in hexanes, 0.67 mmol) in 2.5 mL of THF at 0 °C] in THF (2.5 mL) at −78 °C. After being stirred for 15 min at −78 °C, the solution was allowed to warm to −40 °C over a period of 1 h. The reaction mixture was cooled to −78 °C, and a solution of aldehyde **8** (244 mg, 0.56 mmol, 1.0 equiv) in THF (1.0 mL) was added dropwise. The resulting mixture was stirred for 15 min at −78 °C and then quenched by dropwise addition of saturated aqueous NH_4Cl solution (2 mL). The aqueous phase was extracted with ether (3 × 5 mL), and the combined organic layer was dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided a mixture of aldol products **70**:**71** (354 mg (85%) of ca. 3:1 by ^1H NMR). Separation of these diastereoisomers was carried out by preparative thin-layer chromatography (silica gel, 20% ether in hexanes), leading to pure **70** (270 mg, 64%) and **71** (84 mg, 20%). **70**: colorless oil; R_f = 0.40 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ −17.5 (*c* 0.5, $CHCl_3$); IR (thin film) ν_{max} 3490, 2932, 2873, 1683, 1463, 1385, 1249, 1089, 840, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 1 H, SCH=C), 6.44 (s, 1 H, C*H*=CCH_3), 5.12 (dd, *J* = 7.1, 7.0 Hz , 1 H, $C(CH_3)$=C*H*CH_2), 4.08 (dd, *J* = 6.8, 6.5 Hz, 1 H, $(CH_3)_2$CC*H*OSi), 3.89 (dd, *J* = 7.6, 2.7 Hz, 1 H, CH_2C*H*OSi), 3.69−3.65 (m, 1 H, $CH(CH_3)$C*H*OH), 3.59 (t, *J* = 7.5 Hz, 2 H, CH_2OSi), 3.32−3.27 (m, 1 H, C(O)C*H*(CH_3)), 2.68 (s, 3 H, N=$C(CH_3)$S), 2.30−2.19 (m, 2 H, $C(CH_3)$=CHC*H*$_2$), 2.10−1.90 (m, 2 H, C*H*$_2C(CH_3)$=CH), 1.98 (s, 3 H, CH=$C(CH_3)$), 1.65 (s, 3 H, $C(CH_3)$=$CHCH_2$), 1.80−1.46 (m, 5 H), 1.34−1.25 (m, 2 H), 1.19 (s, 3 H, $C(CH_3)_2$), 1.07 (s, 3 H, $C(CH_3)_2$), 1.01 (d, *J* = 6.8 Hz, 3 H, $CH(CH_3)$), 0.89 (s, 18 H, 2 x $SiC(CH_3)_3$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.81 (d, *J* = 6.8 Hz, 3 H, $CH(CH_3)$), 0.10 (s, 3 H, $Si(CH_3)_2$), 0.08 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 3 H, $Si(CH_3)_2$), 0.02 (s, 6 H, $Si(CH_3)_2$), −0.01 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 222.0, 164.1, 153.1, 142.4, 136.7, 121.3, 118.5, 114.7, 78.9, 74.7, 74.0, 60.3, 53.8, 41.2, 37.7, 35.9, 32.8, 32.5, 32.2, 26.0, 25.9, 25.8, 25.0, 24.9, 23.5, 22.8, 20.4, 19.0, 18.2, 18.1, 18.0, 15.2, 13.8, 9.5, −3.8, −4.2, −4.8, −5.1, −5.4; FAB HRMS (NBA/CsI) *m/e* 970.4620, M + Cs^+ calcd for $C_{45}H_{87}NO_5SSi_3$ 970.4667. **71**: colorless oil; R_f = 0.33 (silica gel, 20% ether in hexanes); IR (thin film) ν_{max} 3490, 2932, 2873, 1683, 1463, 1385, 1249, 1089, 840, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (s, 1 H, SCH=C), 6.44 (s, 1 H, C*H*=CCH_3), 5.16−5.12 (m, 1 H, $C(CH_3)$=C*H*CH_2), 4.09−4.05 (m, 1 H, $(CH_3)_2$CC*H*OSi), 3.65−3.58 (m, 3 H, CH_2C*H*OSi, CH_2OSi), 3.42−3.38 (m, 1 H, $CH(CH_3)$C*H*OH), 3.24−3.19 (m, 1 H, C(O)-C*H*(CH_3)), 2.69 (s, 3 H, N=$C(CH_3)$S), 2.31−2.18 (m, 2 H, $C(CH_3)$=CHC*H*$_2$), 1.98 (s, 3 H, CH=$C(CH_3)$), 1.99−1.88 (m, 2 H, C*H*$_2C(CH_3)$=CH), 1.67 (s, 3 H, $C(CH_3)$=$CHCH_2$), 1.55−1.40 (m, 5 H), 1.35−1.25 (m, 2 H), 1.20 (s, 3 H, $C(CH_3)_2$), 1.13 (s, 3 H, $C(CH_3)_2$), 1.09 (d, *J* = 7.0 Hz, 3 H, $CH(CH_3)$), 0.95 (d, *J* = 7.0 Hz, 3 H, $CH(CH_3)$), 0.88 (s, 18 H, 2 x $SiC(CH_3)_3$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.10 (s, 3 H, $Si(CH_3)_2$), 0.05 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 6 H, $Si(CH_3)_2$), −0.01 (s, 3 H, $Si(CH_3)_2$); FAB HRMS (NBA) *m/e* 838.5653, M + Cs^+ calcd for $C_{45}H_{87}NO_5SSi_3$ 838.5691.

Tetrakis(silyl ether) 72. Compound **70** (275 mg, 0.33 mmol) was dissolved in CH_2Cl_2 (5.0 mL), cooled to 0 °C, and treated with 2,6-lutidine (76 μL, 0.66 mmol, 2.0 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (88 μL, 0.39 mmol, 1.2 equiv). After being stirred for 2 h at 0 °C, the reaction mixture was quenched with aqueous HCl (5 mL, 1.0 N solution) and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic solution was washed with brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 3% ether in hexanes) provided tetrakis(silyl ether) **72** (300 mg, 96%) as a colorless oil. **72**: R_f = 0.56 (silica gel, 10% ether in hexanes); $[\alpha]^{22}_D$ −10.8 (*c* 0.5, $CHCl_3$); IR (thin film) ν_{max} 2919, 2872, 1690, 1461, 1384, 1361, 1249, 1085, 985, 838, 773, 732, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1 H, SCH=C), 6.43 (s, 1 H, C*H*=CCH_3), 5.13 (dd, *J* = 7.1, 7.0 Hz, 1 H, $C(CH_3)$=C*H*CH_2), 4.08 (dd, *J* = 6.8, 6.7 Hz, 1 H, $(CH_3)_2$-CC*H*OSi), 3.89 (dd, *J* = 7.6, 2.7 Hz, 1 H, CH_2C*H*OSi), 3.77 (dd, *J* = 6.7, 1.0 Hz, 1 H, $CH(CH_3)$C*H*OSi), 3.67−3.62 (m, 1 H, CH_2OSi), 3.58−3.53 (m, 1 H, CH_2OSi), 3.14 (dd, *J* = 6.8, 6.7 Hz, 1 H, C(O)-C*H*(CH_3)), 2.68 (s, 3 H, N=$C(CH_3)$S), 2.29−2.17 (m, 2 H, $C(CH_3)$=CHC*H*$_2$), 1.98 (s, 3 H, CH=$C(CH_3)$), 1.97−1.89 (m, 2 H, C*H*$_2C(CH_3)$=CH), 1.64 (s, 3 H, $C(CH_3)$=$CHCH_2$) 1.50−1.45 (m, 5 H), 1.34−1.23 (m, 2 H), 1.20 (s, 3 H, $C(CH_3)_2$), 1.02 (d, *J* = 6.8 Hz, 3 H, $CH(CH_3)$), 1.00 (s, 3 H, $C(CH_3)_2$), 0.88−0.86 (m, 39 H, $CH(CH_3)$, 4 x $SiC(CH_3)_3$), 0.08 (s, 3 H, $Si(CH_3)_2$), 0.07 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 3 H, $Si(CH_3)_2$), 0.02 (s, 6 H, $Si(CH_3)_2$), 0.01 (s, 3 H, $Si(CH_3)_2$), −0.02 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.2, 164.2, 153.2, 142.4, 136.6, 121.5, 118.5, 114.9,

78.8, 77.3, 73.9, 60.9, 53.6, 44.9, 38.8, 37.9, 35.2, 32.4, 30.9, 26.2, 26.1, 25.9, 24.4, 23.4, 19.2, 19.1, 18.5, 18.3, 18.2, 18.1, 17.5, 13.9, −3.7, −3.8, −4.0, −4.7, −4.9, −5.2, −5.3; FAB HRMS (NBA) *m/e* 952.6515, M − H⁺ calcd for $C_{51}H_{101}NO_5SSi_4$ 952.6556.

Alcohol 73. Alcohol 73 (200 mg, 85%) was obtained from compound 72 (264 mg, 0.28 mmol) according to the procedure described above for 35. 73: colorless oil; R_f = 0.25 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ −9.3 (*c* 0.2, $CHCl_3$); IR (thin film) ν_{max} 3392, 2939, 2865, 1689, 1463, 1378, 1357, 1252, 1083, 988, 867, 835, 772, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (s, 1 H, SCH=C), 6.44 (s, 1 H, C*H*=CCH$_3$), 5.14 (dd, *J* = 7.0, 6.9 Hz, 1 H, C(CH$_3$)=C*H*CH$_2$), 4.10−4.05 (m, 2 H, (CH$_3$)$_2$CC*H*OSi, CH$_2$C*H*OSi), 3.78 (dd, *J* = 7.0, 1.0 Hz, 1 H, CH(CH$_3$)C*H*OSi), 3.63 (t, *J* = 7.0 Hz, 2 H, C*H*$_2$OH), 3.11 (dd, *J* = 7.0, 6.8 Hz, 1 H, C(O)C*H*(CH$_3$)), 2.70 (s, 3 H, N=C(CH$_3$)S), 2.27−2.19 (m, 2 H, C(CH$_3$)=CHC*H*$_2$), 1.99 (d, *J* = 1.0 Hz, 3 H, CH=C(C*H*$_3$)), 2.10−1.90 (m, 2 H, C*H*$_2$C(CH$_3$)=CH), 1.65 (s, 3 H, C(C*H*$_3$)=CHCH$_2$), 1.50−1.39 (m, 2 H), 1.36−1.29 (m, 3 H), 1.21 (s, 3 H, C(CH$_3$)$_2$), 1.20−1.10 (m, 2 H), 1.05 (s, 3 H, C(CH$_3$)$_2$), 1.04 (d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)), 0.91−0.87 (m, 30 H, CH(C*H*$_3$), 3 x SiC(CH$_3$)$_3$), 0.11 (s, 3 H, Si(CH$_3$)$_2$), 0.07 (s, 3 H, Si(CH$_3$)$_2$), 0.06 (s, 6 H, Si(CH$_3$)$_2$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), −0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 219.5, 164.2, 153.1, 142.4, 136.6, 121.5, 118.5, 114.8, 78.8, 77.4, 72.9, 60.1, 53.6, 45.8, 44.9, 38.6, 38.2, 35.2, 32.4, 30.6, 26.1, 25.9, 24.7, 23.4, 19.1, 18.4, 18.1, 18.0, 17.6, 15.5, 13.8, −3.7, −3.8, −4.0, −4.7, −5.1; FAB HRMS (NBA/CsI) *m/e* 970.4694, M − Cs⁺ calcd for $C_{45}H_{97}NO_5SSi_3$ 970.4667.

Aldehyde 74. Oxidation of Alcohol 73. To a solution of oxalyl chloride (54 μL, 0.61 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) was added dropwise DMSO (86 μL, 1.21 mmol, 4.0 equiv) at −78 °C. After the mixture was stirred for 15 min at −78 °C, a solution of alcohol 73 (255 mg, 0.305 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added dropwise at −78 °C over a period of 5 min. The solution was stirred at −78 °C for 30 min, and then Et_3N (250 μL, 1.82 mmol, 6.0 equiv) was added. The reaction mixture was allowed to warm to 0 °C over a period of 30 min, and then ether (20 mL) was added, followed by saturated aqueous NH_4Cl solution (10 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided aldehyde 74 (241 mg, 95%) as a colorless oil. 74: R_f = 0.47 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ −12.0 (*c* 0.1, $CHCl_3$); IR (thin film) ν_{max} 2943, 2849, 1725, 1690, 1461, 1384, 1249, 1079, 985, 832, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.74 (m, 1 H, CHO), 6.89 (s, 1 H, SCH=C), 6.43 (s, 1 H, C*H*=CCH$_3$), 5.14 (dd, *J* = 7.1, 7.0 Hz, 1 H, C(CH$_3$)=C*H*CH$_2$), 4.48−4.44 (m, 1 H, (CH$_3$)$_2$CC*H*OSi), 4.07 (dd, *J* = 6.1, 5.3 Hz, 1 H, CH$_2$C*H*OSi), 3.75 (dd, *J* = 7.4, 1.0 Hz, 1 H, CH(CH$_3$)C*H*OSi), 3.11 (dd, *J* = 7.0, 6.7 Hz, 1 H, C(O)C*H*(CH$_3$)), 2.69 (s, 3 H, N=C(CH$_3$)S), 2.50 (ddd, *J* = 16.6, 4.5, 1.0 Hz, 1 H, C*H*$_2$CHO), 2.37 (ddd, *J* = 16.6, 3.2, 1.0 Hz, 1 H, C*H*$_2$CHO), 2.28−2.16 (m, 2 H, C(CH$_3$)=CHC*H*$_2$), 1.97 (s, 3 H, CH=C(C*H*$_3$)), 1.97−1.89 (m, 2 H, C*H*$_2$C(CH$_3$)=CH), 1.64 (s, 3 H, C(C*H*$_3$)=CHCH$_2$), 1.50−1.25 (m, 5 H), 1.22 (s, 3 H, C(CH$_3$)$_2$), 1.05 (s, 3 H, C(CH$_3$)$_2$), 1.01 (d, *J* = 6.9 Hz, 3 H, CH(C*H*$_3$)), 0.89−0.84 (m, 30 H, CH(C*H*$_3$), 3 x SiC(CH$_3$)$_3$), 0.08 (s, 3 H, Si(CH$_3$)$_2$), 0.04 (s, 6 H, Si(CH$_3$)$_2$), 0.03 (s, 3 H, Si(CH$_3$)$_2$), 0.02 (s, 3 H, Si(CH$_3$)$_2$), −0.02 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.5, 201.0, 164.3, 153.2, 142.7, 136.7, 121.5, 118.5, 114.8, 78.9, 77.7, 71.3, 53.4, 45.1, 38.7, 35.3, 32.5, 30.7, 26.2, 25.9, 25.8, 24.1, 23.5, 19.1, 18.7, 18.6, 18.5, 17.7, 15.6, 13.9, −3.6, −3.7, −4.1, −4.5, −4.7, −5.0; FAB HRMS (NBA) *m/e* 836.5500, M + H⁺ calcd for $C_{45}H_{85}NO_5SSi_3$ 836.5535.

Carboxylic Acid 52. Oxidation of Aldehyde 74. Aldehyde 74 (224 mg, 0.29 mmol), ^tBuOH (5.0 mL), isobutylene (5.0 mL, 2 M solution in THF, 10.0 mmol), H_2O (1.0 mL), $NaClO_2$ (90 mg, 0.86 mmol, 3.0 equiv), and NaH_2PO_4 (60 mg, 0.43 mmol, 1.5 equiv) were combined and stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash column chromatography (silica gel, 6% MeOH in CH_2Cl_2) to afford carboxylic acid 52 (220 mg, 90%) whose spectroscopic data were identical with those exhibited by 52 obtained above.

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Supporting Information Available: Selected physical data for compounds 48, 49, 8′, 52′, 53′, and 6′ and $^1H-^1H$ NOESY and $^1H-^1H$ COSY spectra for epoxides 58 and 59 (8 pages). See any current masthead page for ordering and Internet access instructions.

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Mit internationalem Recherchenbericht.

(54) Title: EPOTHILONE DERIVATIVES, PREPARATION AND USE

(54) Bezeichnung: EPOTHILONDERIVATE, HERSTELLUNG UND VERWENDUNG

(57) Abstract

The invention relates to epothilone derivatives and the use thereof.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft Epothilonderivate und deren Verwendung.

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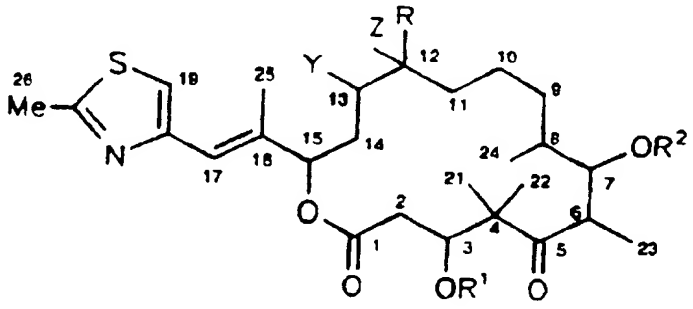
EPOTHILONDERIVATE, HERSTELLUNG UND VERWENDUNG

Die vorliegende Erfindung betrifft allgemein Epothilonderivate und deren Verwendung zur Herstellung von Arzneimitteln. Insbesondere betrifft die vorliegende Erfindung die Herstellung der Epothilonderivate der nachfolgend dargestellten allgemeinen Formeln 1 bis 7 sowie deren Verwendung zur Herstellung von therapeutischen Mitteln und Mitteln für den Pflanzenschutz.



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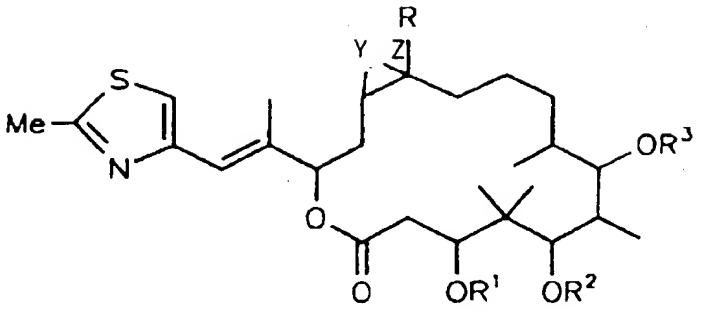

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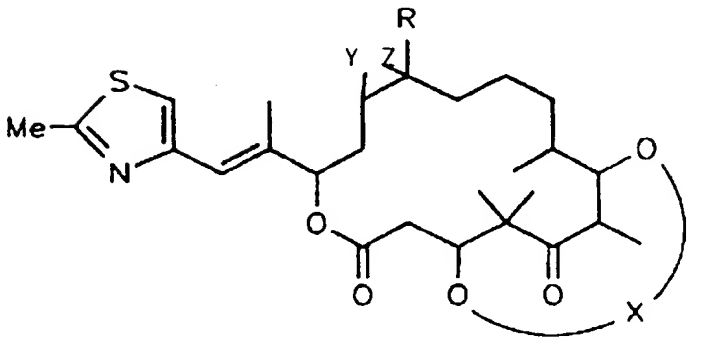

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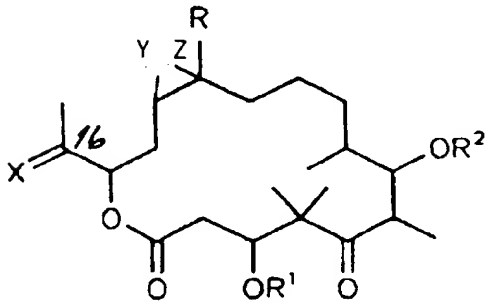

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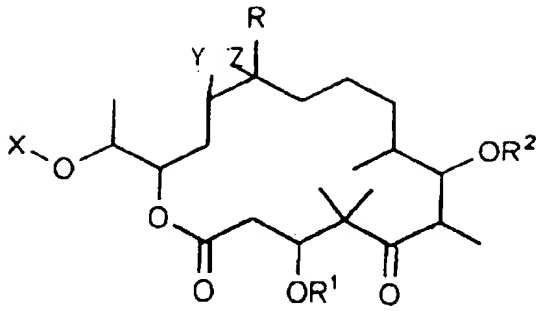

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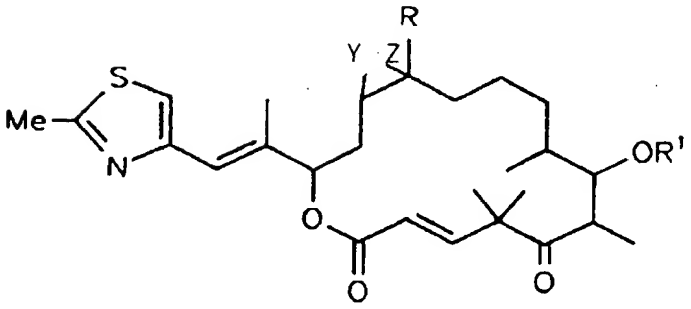

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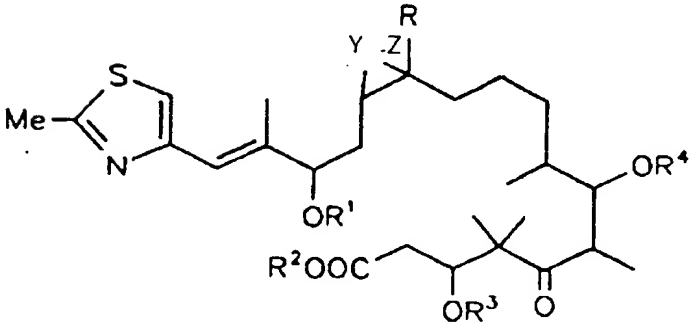


7

In den vorstehenden **Formeln 1 bis Formel 7** bedeuten:

R = H, C_{1-4}-Alkyl;
R^1, R^2, R^3, R^4, R^5 = H, C_{1-6}-Alkyl,
C_{1-6}-Acyl-Benzoyl,
C_{1-4}-Trialkylsilyl,
Benzyl,
Phenyl,
C_{1-6}-Alkoxy-,
C_6-Alkyl-, Hydroxy- und Halogen-substituiertes Benzyl bzw. Phenyl;
wobei auch zwei der Reste R^1 bis R^5 zu der Gruppierung $-(CH_2)_n-$ mit n = 1 bis 6 zusammentreten können und es sich bei den in den Resten enthaltenen Alkyl- bzw. Acylgruppen um gradkettige oder verzweigte Reste handelt;
Y und Z sind entweder gleich oder verschieden und stehen jeweils für Wasserstoff, Halogen, wie F, Cl, Br oder J, Pseudohalogen, wie -NCO, -NCS oder $-N_3$, OH, O-(C_{1-6})-Acyl, O-(C_{1-6})-Alkyl, O-Benzoyl. Y und Z können auch das O-Atom eines Epoxides sein, wobei Epothilon A und B nicht beansprucht werden, oder eine der C-C-Bindungen einer C=C-Doppelbindung bilden.

In der **Formel** 3 steht X allgemein für -C(O)-, -C(S)-, -S(O)-, $-CR^1R^2-$, wobei R^1 und R^2 die Bedeutung haben wie oben angegeben, und $-SiR_2-$, wobei R die Bedeutung hat wie oben angegeben.

In der **Formel** 4 bedeutet X Sauerstoff, NOR^3, $N-NR^4R^5$, und $N-NHCONR^4R^5$, wobei die Reste R^3 bis R^5 die oben angegebene Bedeutung haben.

In der **Formel** 5 bedeutet X Wasserstoff, C_{1-18}-Alkyl, C_{1-18}-Acyl, Benzyl, Benzoyl und Cinnamoyl.

Für Epothilon A und B sei verwiesen auf DE-A-41 38 042. Verbindungen gemäß der allgemeinen **Formel 1** sind ausgehend von Epothilon A und B sowie von deren 3-O- und/oder 7-O-geschützten Derivaten durch Öffnung des 12,13-Epoxids zugänglich. Werden dazu Hydrogenwasserstoffsäuren in einem bevorzugt nicht wässrigen Lösungsmittel eingesetzt, wobei man die Halogenhydrine X = Hal, Y = OH und Y = OH, Y = Hal erhält. Protonensäuren wie z.B. Toluolsulfonsäure und Trifluoressigsäure führen in Gegenwart von Wasser zu 12,13-Diolen, die anschließend nach Standardverfahren acyliert (z.B. mit Carbonsäureanhydriden und Pyridin oder Triethylamin/DMAP) oder alkyliert (Alkylhalogenide und Silberoxid) werden. Die 3- und 7-Hydroxygruppen können dazu vorübergehend als Formiat (Abspaltung mit NH_3/MeOH) oder p-Methoxybenzylether (Abspaltung mit DDQ) geschützt werden.

Verbindungen gemäß der allgemeinen **Formel 2** sind aus Epothilon A und B sowie deren 3-O- und/oder 7-O-geschützten Derivaten durch Reduktion, z.B. mit $NaBH_4$ in Methanol erhältlich. Sind dabei 3-OH und/oder 7-OH reversibel geschützt, so können nach Acylierung oder Alkylierung und Entfernen der Schutzgruppen 5-O-monosubstituierte, 3,5- oder 5,7-O-disubstituierte Derivate der allgemeinen **Formel 2** erhalten werden.

Umsetzungen von Epothilon A und B mit bifunktionellen elektrophilen Reagenzien, wie (Thio)Phosgen, (Thio)Carbonyldimidazol, Thionylchlorid oder Dialkylsilyldichloriden bzw. -bistriflaten ergeben Verbindungen der allgemeinen **Formel 3**. Als Hilfsbasen dienen dabei Pyridin, Trialkylamine, ggf. zusammen mit DMAP bzw. 2,6-Lutidin in einem nichtprotischen Lösungsmittel. Die 3,7-Acetale der allgemeinen **Formel 3** entstehen durch Umacetalisierung z.B. von Dimethylacetalen in Gegenwart eines sauren Katalysators.

Verbindungen gemäß der allgemeinen **Formel 4** werden aus Epothilon A und B oder ihren 3-O- und/oder 7-O-geschützten Derivaten durch Ozonolyse und reduktive Aufarbeitung, z.B. mit Dimethylsulfid, erhalten. Die C-16-Ketone können anschließend nach dem Fachmann geläufigen Standardverfahren in Oxime, Hydrazone oder Semicarbazone umgewandelt werden. Sie werden weiterhin durch Wittig-, Wittig-Horner-, Julia- oder Petersen-Olefinierung in C-16/C-17-Olefine überführt.

Durch Reduktion der C-16-Ketogruppe, z.B. mit einem Aluminium- oder Borhydrid, sind die 16-Hydroxyderivate gemäß der allgemeinen **Formel 5** erhältlich. Diese können, wenn 3-OH und 7-OH mit entsprechenden Schutzgruppen versehen sind, selektiv acyliert oder alkyliert werden. Die Freisetzung der 3-OH- und 7-OH-Gruppen erfolgt z.B. bei O-Formyl durch NH_3/MeOH, bei O-p-Methoxybenzyl durch DDQ.

Die Verbindungen der allgemeinen **Formel 6** werden aus Derivaten von Epothilon A und B erhalten, bei denen die 7-OH-Gruppe durch Acyl- oder Ethergruppen geschützt ist, in dem die 3-OH-Gruppe z.B. formyliert, mesyliert oder tosyliert und anschließend durch Behandlung mit einer Base z.B. DBU eliminiert wird. Die 7-OH-Gruppe kann wie oben beschrieben freigesetzt werden.

Verbindungen der allgemeinen **Formel 7** werden aus Epothilon A und B oder deren 3-OH- und 7-OH-geschützten Derivaten durch basische Hydrolyse erhalten, z.B. mit NaOH in MeOH oder MeOH/Wasser. Vorzugsweise werden Verbindungen der allgemeinen **Formel 7** aus Epothilon A oder B oder deren 3-OH- oder 7-OH-geschützten Derivaten durch enzymatische Hydrolyse erhalten, insbesondere mit Esterasen oder Lipasen. Die Carboxylgruppe kann mit Diazoalkanen nach Schutz der 19-OH-Gruppe durch Alkylierung in Ester umgewandelt werden.

Ferner können Verbindungen der **Formel 7** durch Lactonisierung nach den Methoden von Yamaguchi (Trichlorbenzoylchlorid/DMAP), Corey (Aldrithiol/Triphenylphosphin) oder Kellogg (omega-Bromsäure/Caesiumcarbonat) in Verbindung der **Formel 2** umgewandelt werden. Einschlägige Arbeitsmethoden finden sich bei

Inanaga et al. in Bull. Chem. Soc. Japan, 52 (1979) 1989; Corey & Nicolaou in J. Am. Chem. Soc., 96 (1974) 5614; und Kruizinga & Kellogg in J. Am. Chem. Soc., 103 (1981) 5183.

Zur Herstellung der erfindungsgemäßen Verbindungen kann man auch von Epothilon C oder D ausgehen, wobei zur Derivatisierung auf die vorstehend beschriebenen Derivatisierungsmethoden verwiesen werden kann. Dabei kann man die 12,13-Doppelbindung selektiv hydrieren, beispielsweise katalytisch oder mit Diimin; oder epoxidieren, beispielsweise mit Dimethyldioxiran oder einer Persäure; oder in die Dihalogenide, Dipseudohalogenide oder Diazide umwandeln.

Die Erfindung betrifft ferner Mittel für den Pflanzenschutz in Landwirtschaft, Forstwirtschaft und/oder Gartenbau, bestehend aus einer oder mehreren der vorstehend aufgeführten Epothilonderivate bzw. bestehend aus einem oder mehreren der vorstehend aufgeführten Epothilonderivate neben einem oder mehreren üblichen Träger(n) und/oder Verdünnungsmittel(n).

Schließlich betrifft die Erfindung therapeutische Mittel, bestehend aus einer oder mehreren der vorstehend aufgeführten Verbindungen oder einer oder mehreren der vorstehend aufgeführten Verbindungen neben einem oder mehreren üblichen Träger(n) und/oder Verdünnungsmittel(n). Diese Mittel können insbesondere cytotoxische Aktivitäten zeigen und/oder Immunsuppression bewirken und/oder zur Bekämpfung maligner Tumore eingesetzt werden, wobei sie besonders bevorzugt als Cytostatika verwendbar sind.

Die Erfindung wird im folgenden durch die Beschreibung von einigen ausgewählten Ausführungsbeispielen näher erläutert und beschrieben.

Beispiele

Beispiel 1:
Verbindung 1a

20 mg (0.041 mmol) Epothilon A werden in 1 ml Aceton gelöst, mit 50 µl (0.649 mmol) Trifluoressigsäure versetzt und über Nacht bei 50 °C gerührt. Zur Aufarbeitung wird das Reaktionsgemisch mit 1 M Phosphatpuffer pH 7 versetzt und die wäßrige Phase viermal mit Ethylacetat extrahiert. Die vereinigten organischen Phasen werden mit gesättigter Natriumchlorid-Lösung gewaschen, über Natriumsulfat getrocknet und vom Lösungsmittel befreit. Die Reinigung des Rohproduktes erfolgt mit Hilfe der präparativen Schichtchromatographie (Laufmittel: Dichlormethan/Aceton, 85 : 15).

Ausbeute: 4 mg (19 %) Isomer I
4 mg (19 %) Isomer II

Isomer I

R_f (Dichlormethan/Aceton, 85 : 15): 0.46

IR (Film): ny = 3440 (m, b, Sch), 2946 (s, Sch), 1734 (vs), 1686 (m), 1456 (m), 1375 (w), 1256 (s, Sch), 1190 (w, b, Sch), 1071 (m, Sch), 884 (w), 735 (w) cm^{-1}.

MS (20/70 eV): m/e (%) = 493 (43 $[M-H_2O]^+$), 394 (47), 306 (32), 206 (30), 181 (40), 166 (72), 139 (100), 113 (19), 71 (19), 57 (24), 43 (24).

Hochauflösung: $C_{26}H_{39}O_6NS$ ber.: 493.2498 für $[M-H_2O]^+$
gef.: 493.2478

Isomer II

R_f (Dichlormethan/Aceton, 85 : 15): 0.22

IR (Film): ny = 3484 (s, b, Sch), 2942 (vs, Sch), 1727 (vs), 1570 (w), 1456 (m), 1380 (m), 1265 (s), 1190 (w), 1069 (m), 975 (w), cm^{-1}.

MS (20/70 eV): m/e (%) = 493 (21 $[M-H_2O]^+$), 394 (12), 306 (46), 206 (37), 181 (63), 166 (99), 139 (100), 113 (21), 71 (23), 57 (33), 43 (28).

Hochauflösung: $C_{26}H_{39}O_6NS$ ber.: 493.2498 für $[M-H_2O]^+$
gef.: 493.2475

Beispiel 2:
Verbindung 1b

55 mg (0.111 mmol) Epothilon A werden in 0.5 ml Tetrahydrofuran gelöst, mit 0.S ml 1 N Salzsäure versetzt und 30 Minuten bei Raumtemperatur gerührt. Anschließend wird mit 1 N Phosphatpuffer pH 7 versetzt und die wäßrige Phase viermal mit Ethylacetat extrahiert. Die vereinigten organischen Phasen werden mit gesättigter Natriumchlorid-Lösung gewaschen, über Natriumsulfat getrocknet und vom Lösungsmittel befreit. Die Reinigung des Rohproduktes erfolgt mit Hilfe der präparativen Schichtchromatographie (Laufmittel: Dichlormethan/Methanol, 90 : 10). Ausbeute: 19 mg (32 %)

R_f (Dichlormethan/Methanol, 90 : 10): 0.46

IR (Film): ny = 3441 (s, br, Sch), 2948 (s, Sch), 1725 (vs, Sch), 1462 (m), 1381 (w), 1265 (m), 1154 (w), 972 (m, br, Sch) cm^{-1}.

UV (Methanol): $lambda_{max}$ (lg epsilon) = 210 (4.29), 248 (4.11) nm.

MS (20/70 eV): m/e (%) = 529 (13 [M^+]), 494 (10), 342 (38), 306 (23), 194 (32), 164 (100), 140 (31), 113 (15), 57 (16).

Hochauflösung: $C_{26}H_{40}O_6ClNS$ ber.: 529.2265 für [M^+], gef.: 529.2280

Beispiel 3:
Verbindung 1c

25 mg (0.047 mmol) 12-Chlor-13-hydroxy-epothilon A (**1b**) werden in 1 ml Dichlormethan gelöst, mit 29 mg (0.235 mmol) Dimethylaminopyridin, 151 µl (1.081 mmol) Triethylamin und 20 µl (0.517 mmol) 98 %-iger Ameisensäure versetzt. Das Reaktionsgemisch wird mit Eis/Natriumchlorid abgekühlt. Nach Erreichen von -15 °C werden dem Reaktionsgemisch 40 µl (0.423 mmol) Essigsäureanhydrid zugegeben und 70 Minuten bei -15 °C gerührt. Nachdem ein Dünnschichtchromatogramm keinen vollständigen Umsatz anzeigt, werden dem Reaktionsgemisch weitere 6 mg (0.047 mmol) Dimethylaminopyridin, 7 µl (0.047 mmol) Triethylamin, 2 µl 98 %-ige Ameisensäure (0.047 mmol) und 4 µl (0.047 mmol) Essigsäureanhydrid zugesetzt und 60 Minuten gerührt. Zur Aufarbeitung wird das Reaktionsgemisch auf Raumtemperatur erwärmt, mit 1 M Phosphatpuffer pH 7 versetzt und die wäßrige Phase viermal mit Ethylacetat extrahiert. Die vereinigten

organischen Phasen werden mit gesättigter Natriumchlorid-Lösung gewaschen, über Natriumsulfat getrocknet und vom Lösungsmittel befreit. Die Reinigung des Rohproduktes erfolgt mit Hilfe der präparativen Schichtchromatographie (Laufmittel: Dichlormethan/Aceton, 90 : 10). Ausbeute: 5 mg (18 %)

R_f (Dichlormethan/Aceton. 90 : 10): 0.67

IR (Film): ny = 3497 (w, b, Sch), 2940 (s, b, Sch), 1725 (vs), 1468 (m, b, Sch), 1379 (m), 1265 (s), 1253 (s), 1175 (vs), 972 (m, b, Sch), 737 (s) cm^{-1}

MS (20/70 eV): m/e (%) = 613 (9 [M^+]), 567 (43), 472 (63), 382 (23), 352 (21), 164 (100), 151 (33), 96 (31), 69 (17), 44 (26).

Hochauflösung: $C_{29}H_{40}O_9NSCl$ ber.: 613.2112 für [M^+]
gef.: 613.2131

Beispiel 4:
Verbindung 1d

10 mg (0.020 mmol) Epothilon B werden in 0.5 ml Tetrahydrofuran gelöst, mit 0.5 ml 1 N Salzsäure versetzt und 30 Minuten bei Raumtemperatur gerührt. Anschließend wird mit 1 M Phosphatpuffer pH 7 versetzt und die wäßrige Phase viermal mit Ethylacetat extrahiert. Die vereinigten organischen Phasen werden mit gesättigter Natriumchlorid-Lösung gewaschen, über Natriumsulfat getrocknet und vom Lösungsmittel befreit. Die Reinigung des Rohproduktes erfolgt mit Hilfe der präparativen Schichtchromatographie (Laufmittel: Dichlormethan/Aceton, 85 : 15).
Ausbeute: 1 mg (9 %)

R_f (Dichlormethan/Aceton, 85 : 15): 0.38

MS (20/70 eV): m/e (%) = 543 (3 [M^+]), 507 (14), 320 (19), 234 (9), 194 (17), 182 (23), 164 (100), 140 (22), 113 (14), 71 (13).

Hochauflösung: $C_{27}H_{42}O_6NSCl$ ber.: 543.2421 für [M^+]
gef.: 543.2405

Beispiel 5:
Verbindung 2a

100 mg (0.203 mmol) Epothilon A werden in 4 ml Tetrahydrofuran/1 M Phosphatpuffer pH 7 (1 : 1) gelöst und solange mit Natriumborhydrid (150 mg = 3.965 mmol) versetzt bis das Edukt laut Dünnschichtchromatogramm vollständig abreagiert ist. Anschließend wird mit 1 M Phosphatpuffer pH 7 verdünnt und die wäßrige Phase viermal mit Ethylacetat extrahiert. Die vereinigten organischen Phasen werden mit gesättigter Natriumchlorid-Lösung gewaschen, über Natriumsulfat getrocknet und vom Lösungsmittel befreit. Die Reinigung des Rohproduktes erfolgt durch Kieselchromatographie (Laufmittel: Dichlormethan/Aceton, 95 : 5 - grad - nach Dichlormethan/Aceton, 85 : 15).

Ausbeute: (20 %)

R_f (Dichlormethan/Aceton, 75 : 25): 0.27

IR (Film): ny = 3413 (s, b, Sch), 2965 (vs, Sch), 1734 (vs), 1458 (m, b, Sch), 1383 (m, Sch), 1264 (s, b, Sch), 1184 (m, b, Sch), 1059 (s, Sch), 966 (s), 885 (w), 737 (m) cm^{-1}

MS (20/70 eV): m/e (%) = 495 (6 [M^+]), 477 (8), 452 (12), 394 (9), 364 (16), 306 (49), 194 (19), 178 (35), 164 (100), 140 (40), 83 (21), 55 (27).

Hochauflösung: $C_{26}H_{41}O_6NS$ ber.: 495.2655 für [M^+]
gef.: 495.2623

Beispiel 6:
Verbindung 3a-d (a-d sind Stereoisomere)

100 mg (0.203 mmol) Epothilon werden in 3 ml Pyridin gelöst, mit 50 µl (0.686 mmol) Thionylchlorid versetzt und 15 Minuten bei Raumtemperatur gerührt. Anschließend wird mit 1 M Phosphatpuffer pH 7 versetzt und die wäßrige Phase viermal mit Ethylacetat extrahiert. Die vereinigten organischen Phasen werden mit gesättigter Natriumchlorid-Lösung gewaschen, über Natriumsulfat getrocknet und vom Lösungsmittel befreit. Die Reinigung des Rohproduktes und Trennung der vier Stereoisomeren **3a-d** erfolgt mit Hilfe der präparativen Schichtchromatographie (Laufmittel: Toluol/Methanol, 90 : 10).

Verbindung 3a

Ausbeute: 4 mg (12 %)

R_f (Toluol/Methanol, 90 : 10): 0.50

IR (Film): ny = 2961 (m, b, Sch), 1742 (vs), 1701 (vs), 1465 (m, Sch), 1389 (m, Sch), 1238 (s, Sch), 1210 (vs, Sch), 1011 (s, Sch), 957 (s, b, Sch), 808 (m, Sch), 768 (s, Sch) cm^{-1}

UV (Methanol): $lambda_{max}$ (lg epsilon) = 210 (4.50), 248 (4.35) nm.

MS (20/70 eV): m/e (%) = 539 (40 [M^+]), 457 (22), 362 (16), 316 (27), 222 (30), 178 (30), 164 (100), 151 (43), 96 (38), 69 (29), 55 (28), 43 (20).

Hochauflösung: $C_{26}H_{37}O_7NS_2$ ber.: 539.2011 für [M^+]

Verbindung 3b

Ausbeute: 14 mg (13 %)

R_f (Toluol/Methanol, 90 : 10): 0.44

IR (Film): ny = 2963 (s, br, Sch), 1740 (vs), 1703 (s), 1510 (w), 1464 (m, br, Sch), 1389 (m, Sch), 1240 (s, br, Sch), 1142 (m), 1076 (w), 1037 (w), 1003 (m), 945 (s, br, Sch), 806 (m, Sch), 775 (s), 737 (m) cm^{-1}.

UV (Methanol): $lambda_{max}$ (lg epsilon) = 211 (4.16), 250 (4.08) nm.

MS (20/70 eV): m/e (%) = 539 (27 [M^+]), 475 (17), 322 (41), 306 (67), 222 (16), 206 (17), 194 (19), 178 (32), 164 (100), 151 (33), 125 (18), 113 (15), 96 (39), 81 (23), 64 (58), 57 (42), 41 (19).

Hochauflösung: $C_{26}H_{37}O_7NS_2$ ber.: 539.2011 für [M^+]
gef.: 539.1998

Verbindung 3c

Ausbeute: 4 mg (4 %)

R_f (Toluol/Methanol, 90 : 10): 0.38

MS (20/70 eV): m/e (%) = 539 (51 [M^+]), 322 (22), 306 (53), 222 (36), 178 (31), 164 (100), 151 (41), 96 (25), 81 (20), 69 (26), 55 (25), 41 (25).

Hochauflösung: $C_{26}H_{37}O_7NS_2$ ber.: 539.2011 für [M^+]
gef.: 539.2001

Verbindung 3d

Ausbeute: 1 mg (1 %)

R_f (Toluol/Methanol, 90 : 10): 0.33

MS (20/70 eV): m/e (%) = 539 (69 [M^+]), 322 (35), 306 (51), 222 (41), 178 (31), 164 (100), 151 (46), 96 (31), 81 (26), 69 (34), 55 (33), 41 (35)

Hochauflösung: $C_{26}H_{37}O_7NS_2$ ber.: 539.2011 für [M^+]
gef.: 539.1997

Beispiel 7:
Verbindung 4a

10 mg (0.020 mmol) Epothilon A werden in 2 ml Dichlormethan gelöst, auf -70 °C abgekühlt und anschließend 5 Minuten mit Ozon bis zur schwachen Blaufärbung behandelt. Das resultierende Reaktionsgemisch wird anschließend mit 0.5 ml Dimethylsulfid versetzt und auf Raumtemperatur erwärmt. Zur Aufarbeitung wird das Reaktionsgemisch vom Lösungsmittel befreit und schließlich durch

präparative Schichtchromatographie (Laufmittel Dichlormethan/Aceton/Methanol, 85 : 10 : 5) gereinigt.

Ausbeute: 5 mg (64 %)

R_f (Dichlormethan/Aceton/Methanol, 85 : 10 : 5): 0.61

IR (Film): ny = 3468 (s, br, Sch), 2947 (s, br, Sch), 1734 (vs, Sch), 1458 (w), 1380 (w), 1267 (w), 1157 (w), 1080 (w), 982 (w) cm^{-1}.

UV (Methanol): $lambda_{max}$ (lg epsilon) = 202 (3.53) nm.

MS (20/70 eV): m/e (%) = 398 (2 [M^+]), 380 (4), 267 (14), 249 (17), 211 (20), 193 (26), 171 (34), 139 (34), 111 (40), 96 (100), 71 (48), 43 (50).

Hochauflösung: $C_{21}H_{34}O_7$ ber.: 398.2305 für [M^+]
gef.: 398.2295

Beispiel 8:
Verbindung 6a

10 mg (0.018 mmol) 3,7-Di-O-formyl-epothilon A werden in 1 ml Dichlormethan gelost, mit 27 µl (0.180 mmol) 1,8-Diazabicyclo[5.4.0]undec-7-en (DBU) versetzt und 60 Minuten bei Raumtemperatur gerührt.
Zur Aufarbeitung wird das Reaktionsgemisch mit 1 M Natriumdihydrogenphosphat-Puffer pH 4.5 versetzt und die wäßrige Phase viermal mit Ethylacetat extrahiert. Die vereinigten organischen Phasen werden mit gesättigter Natriumchlorid-Lösung gewaschen, über Natriumsulfat getrocknet und vom Lösungsmittel befreit. Nach Beseitigung des Lösungsmittel wird das resultierende Rohprodukt in 1 ml Methanol gelöst, mit 200 µl einer ammoniakalischen Methanollösung (2 mmol NH_3/ml Methanol) versetzt und über

Nacht bei Raumtemperatur gerührt. Zur Aufarbeitung wird das Lösungsmittel im Vakuum entfernt.

Ausbeute: 4 mg (22 %)

R_f (Dichlormethan/Aceton, 85 : 15): 0.46

IR (Film): ny = 3445 (w, br, Sch), 2950 (vs, br, Sch), 1717 (vs, Sch), 1644 (w), 1466 (m, Sch), 1370 (m, SCh), 1267 (s, br, Sch), 1179 (s, Sch), 984 (s, Sch), 860 (w), 733 (m) cm^{-1}

UV (Methanol): $lambda_{max}$ (lg epsilon) = 210 (4.16) nm.

MS (20/70 eV): m/e (%) = 475 (28 [M^+]), 380 (21), 322 (37), 318 (40), 304 (66), 178 (31), 166 (100), 151 (29), 140 (19), 96 (38), 81 (20), 57 (26).

Hochauflösung: $C_{26}H_{37}O_5NS$ ber.: 475.2392 für [M^+]
gef. 475.2384

Beispiel 9:
Verbindung 6b

50 mg (0.091 mmol) 3,7-Di-O-formyl-epothilon A (werden in 1 ml Dichlorethan gelöst, mit 2 ml (0.013 mol) 1,8-Diazabicyclo[5.4.0]undec-7-en (DBU) versetzt und 12 Stunden bei 90 °C gerührt.
Zur Aufarbeitung wird das Reaktionsgemisch mit 1 M Natriumdihydrogenphosphat-Puffer pH 4.5 versetzt und die wäßrige Phase viermal mit Ethylacetat extrahiert. Die vereinigten organischen Phasen werden mit gesättigter Natriumchlorid-Lösung gewaschen, über Natriumsulfat getrocknet und vom Lösungsmittel befreit.

Die Reinigung des aus zwei Verbindungen bestehenden Rohproduktes erfolgt mittels präparativer Schichtchromatographie (Laufmittel: Dichlormethan/Aceton, 90 : 10).

Ausbeute: 7 mg (15 %)

Substanzcode
R_f (Dichlormethan/Aceton, 90 : 10): 0.62

IR (Film): ny = 2951 (m, br, Sch), 1723 (vs), 1644 (w, br, Sch), 1468 (w), 1377 (w), 1271 (m, br, Sch), 1179 (s), 987 (m, br, Sch), 735 (w, br, Sch) cm^{-1}.

UV (Methanol): $lambda_{max}$ (lg epsilon) = 210 (4.44) nm.

MS (20/70 eV): m/e (%) = 503 (68 [M^+]), 408 (58), 390 (32), 334 (25), 316 (34), 220 (21), 206 (27), 194 (20), 181 (33), 164 (100), 151 (34), 139 (28), 113 (20), 96 (82), 81 (33), 67 (24), 55 (26), 43 (22).

Hochauflösung: $C_{27}H_{37}O_6NS$ ber.: 503.2342 für [M^+]
gef.: 503.2303

Beispiel 10:
Verbindung 6c

5 mg (0.009 mmol) 3,7-Di-O-acetyl-epothilon werden in 1 ml Methanol gelöst, mit 150 µl einer ammoniakalischen Methanollösung (2 mmol NH_3/ml Methanol) versetzt und über Nacht bei 50 °C gerührt.
Zur Aufarbeitung wird das Lösungsmittel im Vakuum entfernt. Die Reinigung des Rohproduktes erfolgt mit Hilfe der präparativen Schichtchromatographie (Laufmittel: Toluol/Methanol, 90 : 10).

Ausbeute: 3 mg (67 %)

R_f (Dichlormethan/Aceton, 90 : 10): 0.55

IR (Film): ny = 2934 (s, b, Sch), 1719 (vs, b, Sch), 1641 (m), 1460 (m, Sch), 1372 (s, Sch), 1237 (vs, b, Sch), 1179 (s, Sch), 1020 (s), 963 (s, Sch), 737 (vs) cm^{-1}.

UV (Methanol): $lambda_{max}$ (lg epsilon) = 210 (4.33) nm.

MS (20/70 eV): m/e (%) = 517 (57 [M^+]), 422 (58), 318 (31), 194 (20), 181 (34), 166 (100), 151 (31), 96 (96), 81 (32), 69 (27), 55 (29), 43 (69).

Hochauflösung: $C_{28}H_{39}O_6NS$ ber.: 517.2498 für [M^+]
gef.: 517 2492

Beispiel 11:
Verbindung 7a

20 mg (0.041 mmol) Epothilon werden in 0.5 ml Methanol gelöst, mit 0.5 ml 1 N Natronlauge versetzt und 5 Minuten bei Raumtemperatur gerührt.
Zur Aufarbeitung wird das Reaktionsgemisch mit 1 M Phosphatpuffer pH 7 versetzt und die wäßrige Phase viermal mit Ethylacetat extrahiert. Die vereinigten organischen Phasen werden mit gesättigter Natriumchlorid-Lösung gewaschen, über Natriumsulfat getrocknet und vom Lösungsmittel befreit. Die Reinigung des Rohproduktes erfolgt mit Hilfe der präparativen Schichtchromatographie (Laufmittel: Dichlormethan/Methanol, 85 : 15).

Ausbeute: 11 mg (52 %)

R_f (Dichlormethan/Methanol, 85 : 15): 0.92

IR (Film): ny = 3438 (s, br, Sch), 2971 (vs, br, Sch), 1703 (vs), 1507 (m), 1460 (s, Sch), 1383 (m, Sch), 1254 (w), 1190 (w, br, Sch), 1011 (w, br, Sch), 866 (w, br), 729 (s) cm^{-1}

MS (20/70 eV): m/e (%) = 423 (0.1 [M^+]), 323 (4), 168 (89), 140 (100), 85 (31), 57 (67).

Hochauflösung: $C_{23}H_{37}O_4NS$ ber.: 423.2443 für [M^+]
gef.: 423.2410

Beispiel 12:
Verbindung 7b

5 mg (0.009 mmol) 7-O-Acetyl-epothilon werden in 1 ml Methanol gelöst, mit 200 µl einer ammoniakalischen Methanollösung (2 mmol NH_3/ml Methanol) versetzt und zwei Tage bei 50 °C gerührt. Zur Aufarbeitung wird das Lösungsmittel im Vakuum entfernt. Die Reinigung des Rohproduktes erfolgt mit Hilfe der präparativen Schichtchromatographie (Laufmittel: Toluol/Methanol, 90 : 10).

Ausbeute: 3 mg (59 %)

R_f (Dichlormethan/Methanol, 90 : 10): 0.63

IR (Film): ny = 3441 (m, b, Sch), 2946 (s, Sch), 1732 (vs), 1600 (w), 1451 (m), 1375 (m), 1246 (s, b, Sch), 1013 (m, b, Sch) cm^{-1}

UV (Methanol): $lambda_{max}$ (lg epsilon) = 211 (3.75), 247 (3.59) nm.

MS (20/70 eV): m/e (%) = 567 (1 [M^+]), 465 (4), 422 (7), 388 (5), 194 (5), 182 (7), 168 (65), 164 (17), 140 (100), 97 (10), 71 (22), 43 (27).

Hochauflösung: $C_{29}H_{45}O_8NS$ ber.: 567.2866 für [M^+]
gef.: 567.2849

Beispiel 13:

50 mg Epothilon A werden in 20 µl Dimethylsulfoxid angelöst und mit 30 ml Phosphatpuffer (pH 7,1, 30 mM) verdünnt. Nach Zugabe von 5 mg Schweineleberesterase (Fa. Boehringer Mannheim) wird 2 Tage bei 30 °C gerührt. Man säuert mit 2 N HCl auf pH 5 an und extrahiert die Epothilonsäure 7 mit Ethylacetat. Die organische Phase wird mit Natriumsulfat getrocknet, im Vakuum zur Trockne eingedampft. Ausbeute 48 mg (96 %).

Beispiel 14:

48 mg Epothilonsäure 7 werden in 6 ml THF abs. gelöst und unter Rühren mit 40 µl Triethylamin und 16 µl 2,4,6-Trichlorbenzoylchlorid versetzt. Nach 15 min wird vom Niederschlag abfiltriert und innerhalb von 15 min unter schnellem Rühren in eine siedende Lösung von 20 mg 4-Dimethylaminopyridin in 200 ml Toluol abs. getropft. Nach weiteren 10 min wird im Vakuum eingedampft und der Rückstand zwischen Ethylacetat/Citratpuffer (pH 4) verteilt. Der Eindampfrückstand der organischen Phase ergibt nach präparativer HPLC Trennung 15 mg Epothilon A.

Beispiel 15:
Epothilone C und D als Ausgangsverbindungen

A. Produktionsstamm und Kulturbedingungen entsprechend dem Epothilon Basispatent.

B. Produktion mit DSM 6773

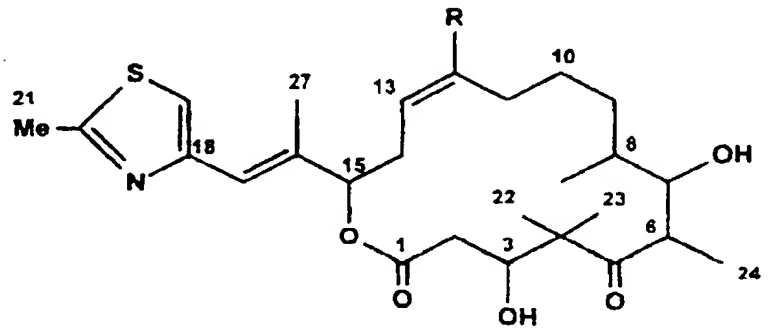
75 l Kultur werden wie im Basispatent beschrieben angezogen und zum Animpfen eines Produktionsfermenters mit 700 l Produktionsmedium aus 0.8 % Stärke, 0.2 % Glukose, 0.2 % Soyamehl, 0.2 % Hefeextrakt, 0.1 % $CaCl_2 \times 2H_2O$, 0.1 % $MgSO_4 \times 7H_2O$, 8 mg/l Fe-EDTA, pH = 7.4 und optional 15 l Adsorberharz Amberlite XAD-16 verwendet. Die Fermentation dauert 7 - 10 Tage bei 30 C, Belüftung mit 2 m^3 Luft/h. Durch Regulierung der Drehzahl wird der pO_2 bei 30 % gehalten.

C. Isolierung

Das Adsorberharz wird mit einem 0.7 m^2, 100 mesh Prozeßfilter von der Kultur abgetrennt und durch Waschen mit 3 Bettvolumen Wasser/Methanol 2:1 von polaren Begleitstoffen befreit. Durch Elution mit 4 Bettvolumen Methanol wird ein Rohextrakt gewonnen, der i. Vak. bis zum Auftreten der Wasserphase eingedampft wird. Diese wird dreimal mit dem gleichen Volumen Ethylacetat extrahiert. Eindampfen der organischen Phase ergibt 240 g Rohextrakt, der zwischen Methanol und Heptan verteilt wird, um lipophile Begleitstoffe abzutrennen. Aus der Methanolphase werden durch Eindampfen i. Vak. 180 g Raffinat gewonnen, das in drei Portionen über Sephadex LH-20 (Säule 20 x 100 cm, 20 ml/min Methanol) fraktioniert wird. Die Epothilone sind in der mit 240 - 300 min Retentionszeit eluierten Fraktion von insgesamt 72 g enthalten. Zur Trennung der Epothilone wird in drei Portionen an Lichrosorb RP-18 (15 µm, Säule 10 x 40 cm, Laufmittel 180 ml/min

Methanol/Wasser 65:35) chromatographiert. Nach Epothilon A und B werden mit R_t = 90-95 min Epothilon C und 100-110 min Epothilon D eluiert und nach Eindampfen i. Vak. in einer Ausbeute von jeweils 0.3 g als farblose Öle gewonnen.

D. Physikalische Eigenschaften



Epothilon C R = H
Epothilon D R = CH_3

Epothilon C

$C_{26}H_{39}NO_5S$ [477]
ESI-MS: (positiv Ionen): 478.5 für $[M+H]^+$

1H und 13C siehe NMR-Tabelle

DC:R_f = 0,82
DC-Alufolie 60 F 254 Merck, Laufmittel: Dichlormethan/Methanol = 9:1
Detektion: UV-Löschung bei 254 nm. Ansprühen mit Vanillin-Schwefelsäure-Reagenz, blau-graue Anfärbung beim Erhitzen auf 120 °C.

HPLC:R_t = 11,5 min
Säule: Nucleosil 100 C-18 7µm, 125 x 4 mm

Laufmittel: Methanol/Wasser = 65:35
Fluß: 1ml/min
Detection: Diodenarray

Epothilon D

$C_{27}H_{41}NO_5S$ [491]
ESI-MS: (positiv Ionen): 492,5 für $[M+H]^+$

1H und 13C siehe NMR-Tabelle

DC:R_f = 0,82
DC-Alufolie 60 F 254 Merck, Laufmittel: Dichlormethan/Methanol = 9:1
Detektion: UV-Löschung bei 254 nm. Ansprühen mit Vanillin-Schwefelsäure-Reagenz, blau-graue Anfärbung beim Erhitzen auf 120 °C.

HPLC:R_t = 15,3 min
Säule: Nucleosil 100 C-18 7µm, 125 x 4 mm
Laufmittel: Methanol/Wasser = 65:35
Fluß: 1ml/min
Detection: Diodenarray

Tabelle: ^1H-und ^{13}C-NMR Daten von Epothilon C und Epothilon D in [D_6]DMSO bei 300 MHz

	Epothilon C			Epothilon D		
H-Atom	δ (ppm)	C-Atom	δ (ppm)	δ (ppm)	C-Atom	δ (ppm)
		1	170.3		1	170.1
2-Ha	2.38	2	38.4	2.35	2	39.0
2-Hb	2.50	3	71.2	2.38	3	70.8
3-H	3.97	4	53.1	4.10	4	53.2
3-OH	5.12	5	217.1	5.08	5	217.4
6-H	3.07	6	45.4	3.11	6	44.4
7-H	3.49	7	75.9	3.48	7	75.5
7-OH	4.46	8	35.4	4.46	8	36.3
8-H	1.34	9	27.6	1.29	9	29.9
9-Ha	1.15	10	30.0	1.14	10	25.9
9-Hb	1.40	11	27.6	1.38	11	31.8*
10-Ha	1.15*	12	124.6	1.14*	12	138.3
10-Hb	1.35*	13	133.1	1.35*	13	120.3
11-Ha	1.90	14	31.1	1.75	14	31.6*
11-Hb	2.18	15	76.3	2.10	15	76.6
12-H	5.38**	16	137.3		16	137.2
13-H	5.44**	17	119.1	5.08	17	119.2
14-Ha	2.35	18	152.1	2.30	18	152.1
14-Hb	2.70	19	117.7	2.65	19	117.7
15-H	5.27	20	164.2	5.29	20	164.3
17-H	6.50	21	18.8	6.51	21	18.9
19-H	7.35	22	20.8	7.35	22	19.7
21-H_3	2.65	23	22.6	2.65	23	22.5
22-H_3	0.94	24	16.7	0.90	24	16.4
23-H_3	1.21	25	18.4	1.19	25	18.4
24-H_3	1.06	27	14.2	1.07	26	22.9
25-H_3	0.90			0.91	27	14.1
26-H_3				1.63		
27-H_3	2.10			2.11		

*, ** Zuordnung vertauschbar

Beispiel 15:
Epothilon A und 12,13-Bisepi-epothilon A aus Epothilon C

50 mg Epothilon A werden in 1.5 ml Aceton gelöst und mit 1.5 ml einer 0.07 molaren Lösung von Dimethyldioxiran in Aceton versetzt. Nach 6 Stunden Stehen bei Raumtemperatur wird i. Vak. eingedampft und durch präparative HPLC an Kieselgel (Laufmittel: Methyl-tert.butylether/Petrolether/Methanol 33:66:1) getrennt.

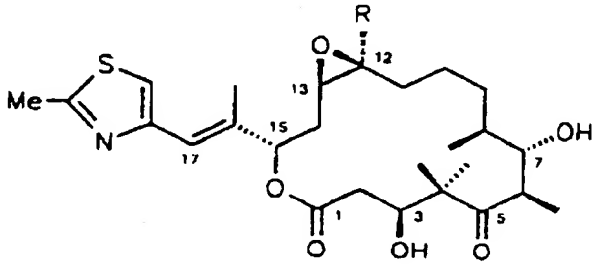
Ausbeute:

25 mg Epothilon A, R_t = 3,5 min (analyt. HPLC, 7 µm, Säule 4 x 250 mm, Laufmittel s. o., Fluß 1.5 ml/min)

und

20 mg 12,13-Bisepi-epothilon A, R_t = 3.7 min, ESI-MS (pos. Ionen)

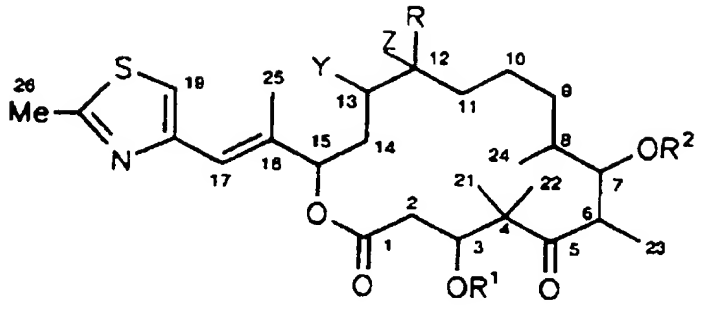
m/z = 494 $[M+H]^+$
^1H-NMR in $[D_4]$ Methanol, ausgewählte Signale: delta = 4.32 (3-H), 3.79 (7-H), 3.06 (12-H), 3.16 (13-H), 5.54 (15-H), 6.69 (17-H), 1.20 (22-H), 1.45 (23-H).



12,13-Bisepi-epothilon A R = H

Patentansprüche

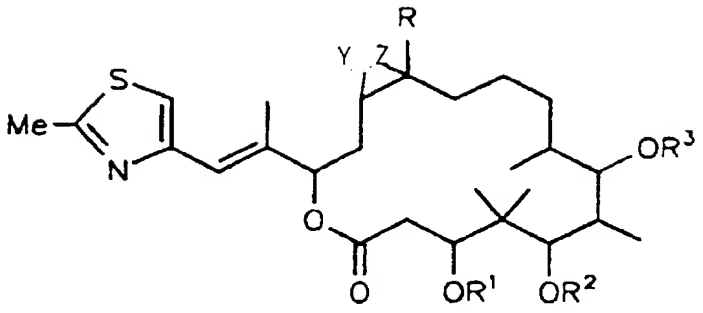
1. Epothilonderivat der Formel 1



1

wobei R = H, C_{1-4}-Alkyl; R^1, R^2 = H, C_{1-6}-Alkyl, C_{1-6}-Acyl, Benzoyl, C_{1-4}-Trialkylsilyl, Benzyl, Phenyl, C_{1-6}-Alkoxy-, C_6-Alkyl-, Hydroxy- und halogensubstituiertes Benzyl bzw. Phenyl; und es sich bei den in den Resten enthaltenen Alkyl- bzw. Acylgruppen um gradkettige oder verzweigte Reste handelt, und Y und Z entweder gleich oder verschieden sind und jeweils für Wasserstoff, Halogen, Pseudohalogen, OH, O-(C_{1-6})-Acyl, O-(C_{1-6})-Alkyl oder O-Benzoyl stehen oder gemeinsam das O-Atom eines Epoxids oder eine der C-C-Bindungen einer C=C-Doppelbindung bilden, wobei Epothilon A und B ausgenomen sind.

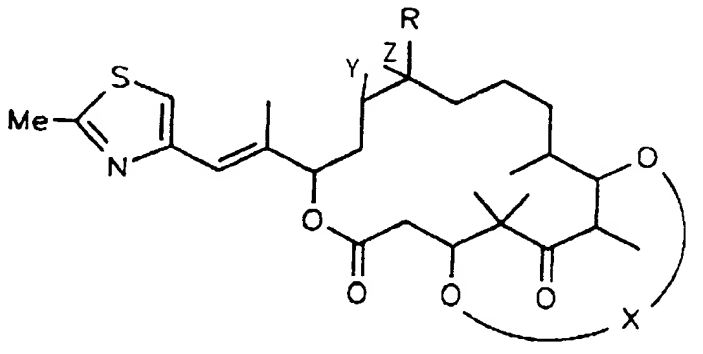
2. Epothilonderivat der Formel 2



2

wobei R = H, C_{1-4}-Alkyl; R^1, R^2, R^3 = H, C_{1-6}-Alkyl, C_{1-6}-Acyl, Benzoyl, C_{1-4}-Trialkylsilyl, Benzyl, Phenyl, C_{1-6}-Alkoxy-, C_6-Alkyl-, Hydroxy- und halogensubstituiertes Benzyl bzw. Phenyl; es sich bei den in den Resten enthaltenen Alkyl- bzw. Acylgruppen um gradkettige oder verzweigte Reste handelt; und Y und Z die Bedeutungen gemäß Anspruch 1 besitzen.

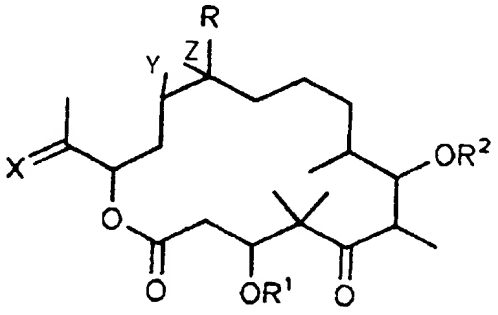
3. Epothilonderivat der Formel 3



3

wobei R = H, C_{1-4}-Alkyl; R^1, R^2 = H, C_{1-6}-Alkyl, C_{1-6}-Acyl, Benzoyl, C_{1-4}-Trialkylsilyl, Benzyl, Phenyl, C_{1-6}-Alkoxy-, C_6-Alkyl-, Hydroxy- und halogensubstituiertes Benzyl bzw. Phenyl; es sich bei den in den Resten enthaltenen Alkyl- bzw. Acylgruppen um gradkettige oder verzweigte Reste handelt, und X allgemein für -C(O)-, -C(S)-, -S(O)-, $-CR^1R^2-$ und $-SiR_2-$ steht, wobei R, R^1 und R^2 die Bedeutung haben wie oben angegeben und R^1 und R^2 auch zusammen eine Alkylengruppe mit 2 bis 6 Kohlenstoffatomen bilden können; und Y und Z die Bedeutungen gemäß Anspruch 1 besitzen.

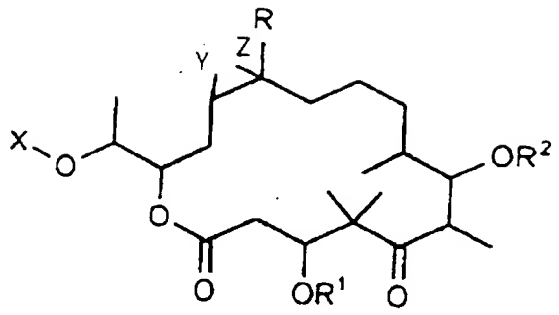
4. Epothilonderivat der Formel 4



4

wobei R = H, C_{1-4}-Alkyl; R^1, R^2, R^3, R^4, R^5 = H, C_{1-6}-Alkyl, C_{1-6}-Acyl, Benzoyl, C_{1-4}-Trialkylsilyl, Benzyl, Phenyl, C_{1-6}-Alkoxy-, C_6-Alkyl-, Hydroxy- und halogensubstituiertes Benzyl bzw. Phenyl; es sich bei den in den Resten enthaltenen Alkyl- bzw. Acylgruppen um gradkettige oder verzweigte Reste handelt, X Sauerstoff, NOR^3, $N-NR^4R^5$, und $N-NHCONR^4R^5$ bedeutet, wobei die Reste R^3 bis R^5 die oben angegebene Bedeutung haben und R^4 und R^5 auch zusammen eine Alkylengruppe mit 2 bis 6 Kohlenstoffatomen bilden können; und
Y und Z die Bedeutungen gemäß Anspruch 1 besitzen.

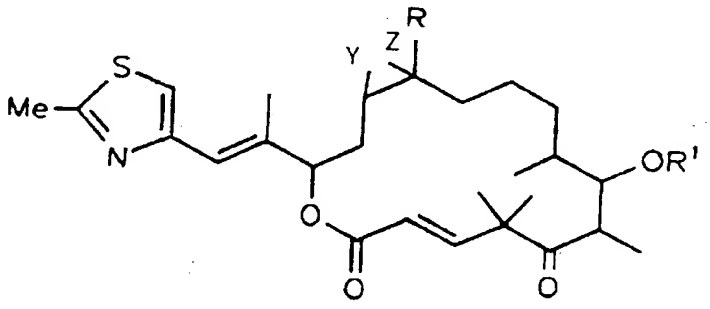
5. Epothilonderivat der Formel 5



5

wobei R = H, C_{1-4}-Alkyl; R^1, R^2 = H, C_{1-6}-Alkyl, C_{1-6}-Acyl, Benzoyl, C_{1-4}-Trialkylsilyl, Benzyl, Phenyl, C_{1-6}-Alkoxy-, C_6-Alkyl-, Hydroxy- und halogensubstituiertes Benzyl bzw. Phenyl; es sich bei den in den Resten enthaltenen Alkyl- bzw. Acylgruppen um gradkettige oder verzweigte Reste handelt, und X Wasserstoff, C_{1-18}-Alkyl, C_{1-18}-Acyl, Benzyl, Benzoyl und Cinnamoyl bedeutet und
Y und Z die Bedeutungen gemäß Anspruch 1 besitzen.

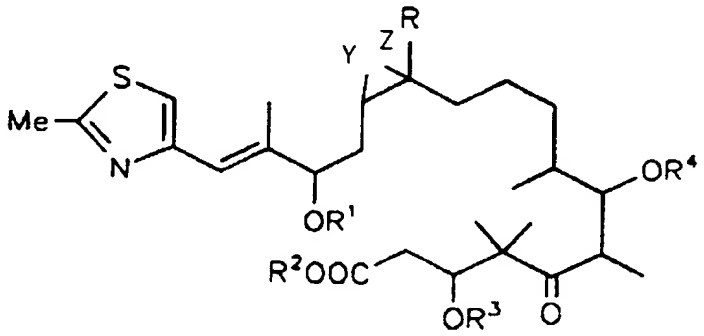
6. Epothilonderivat der Formel 6



6

wobei R = H, C_{1-4}-Alkyl und R^1 = H, C_{1-6}-Alkyl, C_{1-6}-Acyl, Benzoyl, C_{1-4}-Trialkylsilyl, Benzyl, Phenyl, C_{1-6}-Alkoxy-, C_6-Alkyl-, Hydroxy- und halogensubstituiertes Benzyl bzw. Phenyl ist; es sich bei den in den Resten enthaltenen Alkyl- bzw. Acylgruppen um gradkettige oder verzweigte Reste handelt; und Y und Z die Bedeutungen gemäß Anspruch 1 besitzen.

7. Epothilonderivat der Formel 7



7

wobei R = H, C_{1-4}-Alkyl und R^1, R^2, R^3, R^4 = H, C_{1-6}-Alkyl, C_{1-6}-Acyl, Benzoyl, C_{1-4}-Trialkylsilyl, Benzyl, Phenyl, C_{1-6}-Alkoxy, C_6-Alkyl-, Hydroxy- und halogensubstituiertes Benzyl bzw. Phenyl; es sich bei den in den Resten enthaltenen Alkyl- bzw. Acylgruppen um gradkettige oder verzweigte Reste handelt; und Y und Z die Bedeutungen gemäß Anspruch 1 besitzen.

8. Verfahren zur Herstellung eines Epothilonderivats der Formel 7 gemäß Anspruch 7, dadurch ***gekennzeichnet***, daß man Epothilon A, Epothilon B, ein 3-OH-geschütztes Derivat derselben oder ein 7-OH-geschütztes Derivat derselben

(a) enzymatisch hydrolysiert, insbesondere mit einer Esterase oder Lipase, oder
(b) in alkalischem Medium hydrolysiert, insbesondere mit Natriumhydroxid in einem Methanol/Wasser-Gemisch,
und das Epothilonderivat der Formel 7 gewinnt und isoliert.

9. Verfahren zur Herstellung eines Epothilonderivats der Formel 2 gemäß Anspruch 2, dadurch ***gekennzeichnet,*** daß man ein Epothilonderivat der Formel 7 gemäß Anspruch 7 oder als Produkt des Verfahrens gemäß Anspruch 8
(a) nach der Yamaguchi-Methode oder
(b) nach der Corey-Methode oder
(c) nach der Kellogg-Methode
in das Epothilonderivat der Formel 2 umwandelt und dieses Umwandlungsprodukt isoliert.

10. Verfahren zur Herstellung von Epothilon A und/oder 12,13-Bisepi-epothilon A, dadurch **gekennzeichnet**, daß man Epothilon C epoxidiert, insbesondere mit Dimethyldioxiran oder einer Persäure.

11. Verfahren zur Herstellung von Epothilon B und/oder 12,13-Bisepi-epothilon B, dadurch **gekennzeichnet**, daß man Epothilon D epoxidiert, insbesondere mit Dimethyldioxiran oder einer Persäure.

12. Mittel für den Pflanzenschutz in der Landwirtschaft und Forstwirtschaft und/oder im Gartenbau, bestehend aus einem oder mehreren der Verbindungen gemäß einem der vorangehenden Ansprüche oder einer oder mehreren dieser Verbindungen neben einem oder mehreren üblichen Träger(n) und/oder Verdünnungsmittel(n).

13. Therapeutisches Mittel, insbesondere zum Einsatz als Cytostatikum, bestehend aus einer oder mehrerer der Verbindungen nach einem oder mehreren der Ansprüche 1 bis 7 oder einer oder

mehrerer der Verbindungen nach einem oder mehreren der Ansprüche 1 bis 7 neben einem oder mehreren üblichen Träger(n) und/oder Verdünnungsmittel(n).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/05080

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D493/04 C07D417/06 C07D277/24 A61K31/425 C07F7/08
C07D493/08 A01N43/78 A01N43/90 //(C07D493/04,313:00,
303:00),(C07D493/08,321:00,313:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 10121 A (GESELLSCHAFT FÜR BIOTECHNOLOGISHE FORSCHUNG MBH)) 27 May 1993 see claims -----	1-13

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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2

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 1997	13. 02. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (- 31-70) 340-2040, Tx. 31 651 epo nl, Fax (- 31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 96/05080

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9310121	27-05-93	DE-A- 4138042	27-05-93
		AU-A- 2943792	15-06-93

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 96/05080

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 C07D493/04 C07D417/06 C07D277/24 A61K31/425 C07F7/08
C07D493/08 A01N43/78 A01N43/90 //(C07D493/04,313:00,
303:00),(C07D493/08,321:00,313:00)

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 C07D C07F

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	WO 93 10121 A (GESELLSCHAFT FÜR BIOTECHNOLOGISHE FORSCHUNG MBH)) 27.Mai 1993 siehe Ansprüche -----	1-13

☐ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

☒ Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :

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"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

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Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
10.Februar 1997	13. 02. 97
Name und Postanschrift der Internationale Recherchenbehörde Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Bevollmächtigter Bediensteter Henry, J

Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlich. „en, d[redacted] selben Patentfamilie gehoren

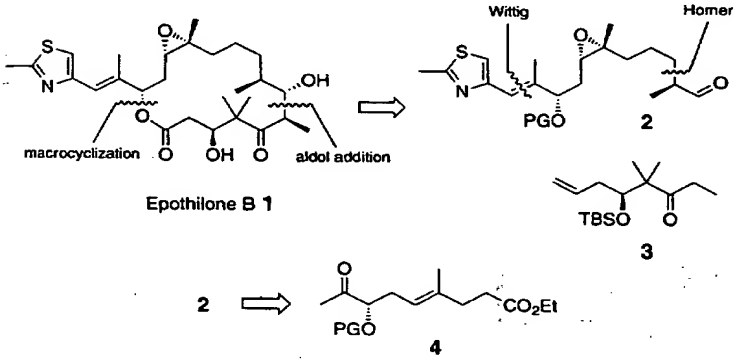
Inte[redacted]ales Aktenzeichen
PCT/EP 96/05080

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
WO-A-9310121	27-05-93	DE-A-	4138042	27-05-93
		AU-A-	2943792	15-06-93

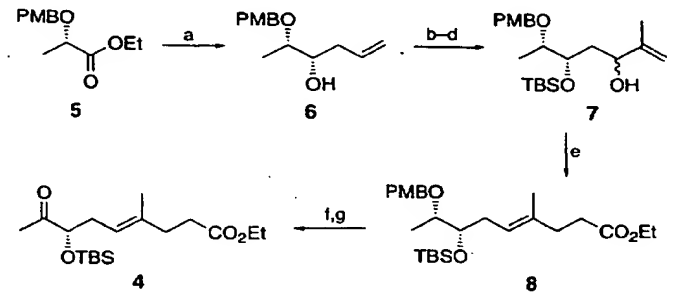
How Stable Are Epoxides? A Novel Synthesis of Epothilone B**

Harry J. Martin, Martina Drescher, and Johann Mulzer*

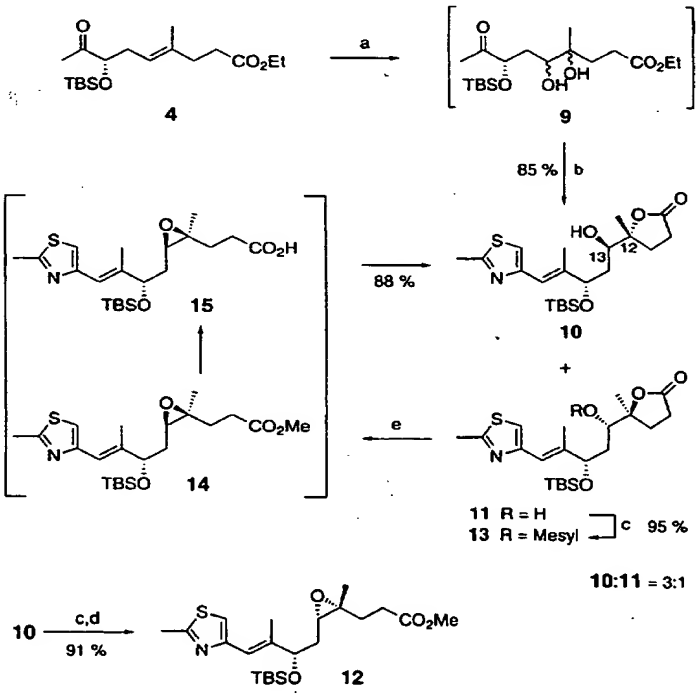
Epothilone B (**1**), a novel antitumor agent,[1] features a trisubstituted epoxide as a central structural element, whose precise contribution to the biological activity is not yet clear.[2] In all syntheses of **1** so far,[3] the corresponding (*Z*)-olefin (epothilone D) was epoxidized in the last step with diastereoselectivies between 4:1 and 20:1 in favor of the desired β isomer. This strategy has been chosen obviously to avoid undesired additions to a presumably labile epoxide. We wanted to test the alleged lability of the epoxide by a new synthesis in which the epoxide is introduced at a very early stage and then deliberately carried through the hardships of a multistep synthesis. The key step of our synthesis featured an aldol addition of epoxyaldehyde **2** to the known ketone **3**[3b] (Scheme 1). Fragment **2** was to be obtained from the (*E*)-enoate **4** readily available from (*S*)-ethyllactate **5** (Scheme 2) which was reduced to the aldehyde and submitted to a chelate-controlled allyl addition to give **6**. Chain elongation produced allylic alcohol **7** which was used in a Johnson Claisen rearrangement to furnish (*E*)-olefin **8** as a single stereoisomer. In the conversion of the ester **4** into the key building block **2** it is particularly important to avoid the introduction of O^- and OH functions in γ-position to one of the epoxide carbon atoms, since, as previous studies have shown, otherwise opening of the epoxide is inevitable. Removal of the *p*-methoxybenzyl (PMB) group and Swern oxidation delivered ketone **4**, which on asymmetric dihydroxylation[4] furnished diol **9** as an inseparable mixture of isomers. Without purification, this mixture was converted into olefins **10** and **11** by a Wittig reaction. After chromatographic separation, **10** was mesylated and treated with potassium carbonate in methanol to give the desired epoxide **12** (Scheme 3). In contrast to the highly (*E*)-selective (>98:2)



Scheme 1. Retrosynthetic analysis. PG = protective group, TBS = *tert*-butyldimethylsilyl.



Scheme 2. Synthesis of (*E*)-olefin **4**: a) 1 equiv DIBAL, CH_2Cl_2, −78 °C, 2 h, 1 equiv $MgBr_2 \cdot Et_2O$, then 2 equiv Allyl-MgBr, −78 to 20 °C, 12 h, 92 %, diastereoselectivity 9:1; b) 1.4 equiv TBSCl, 4 equiv imidazole, DMF, 22 °C, 24 h, 98 %; c) O_3, CH_2Cl_2/MeOH (15:1) −78 °C, then PPh_3, 96 %; d) isopropenyl-MgBr, THF, −10 °C, 45 min, 89 % as a 1:1 mixture of diastereomers; e) 8 equiv triethylorthoacetate, $C_2H_5CO_2H$ (catalytic amount), xylene, 140 °C, 12 h, 95 %, only *E* isomer; f) 1.1 equiv DDQ, CH_2Cl_2/H_2O (19:1), 0.5 h, 94 %; g) 2.5 equiv $(COCl)_2$, 4 equiv DMSO, 6 equiv NEt_3, −78 °C, 97 %. DIBAL = diisobutylaluminum hydride; DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone; DMSO = dimethyl sulfoxide; PMB = *p*-methoxybenzyl.



Scheme 3. Synthesis of the *cis*-epoxide **12**: a) AD-mix-β, methanesulfonamide, *t*BuOH/H_2O (1:1), room temperature, 20 h; b) 2.2 equiv (2-methylthiazol-4-ylmethyl)-tributylphosphonium chloride, 2.2 equiv KHMDS, THF, −78 °C, 0.5 h, then **9**, −78 to 35 °C, 5 min, 78–85 % over two steps, **10**:**11** ca. 3:1; c) 2 equiv MsCl, 2.5 equiv NEt_3, CH_2Cl_2, −15 °C, 3 h; d) 2 equiv K_2CO_3, MeOH, 0.75 h, 91 % over two steps; e) 2 equiv K_2CO_3, MeOH, room temperature, 1 h; 2 equiv K_2CO_3 MeOH/H_2O, 36 h; extraction with aqueous HCl (1N)/CH_2Cl_2, then silica gel, CH_2Cl_2, 3 d, 88 %. KHMDS = potassium bis(trimethylsilyl)amide; Ms = mesyl = methanesulfonyl.

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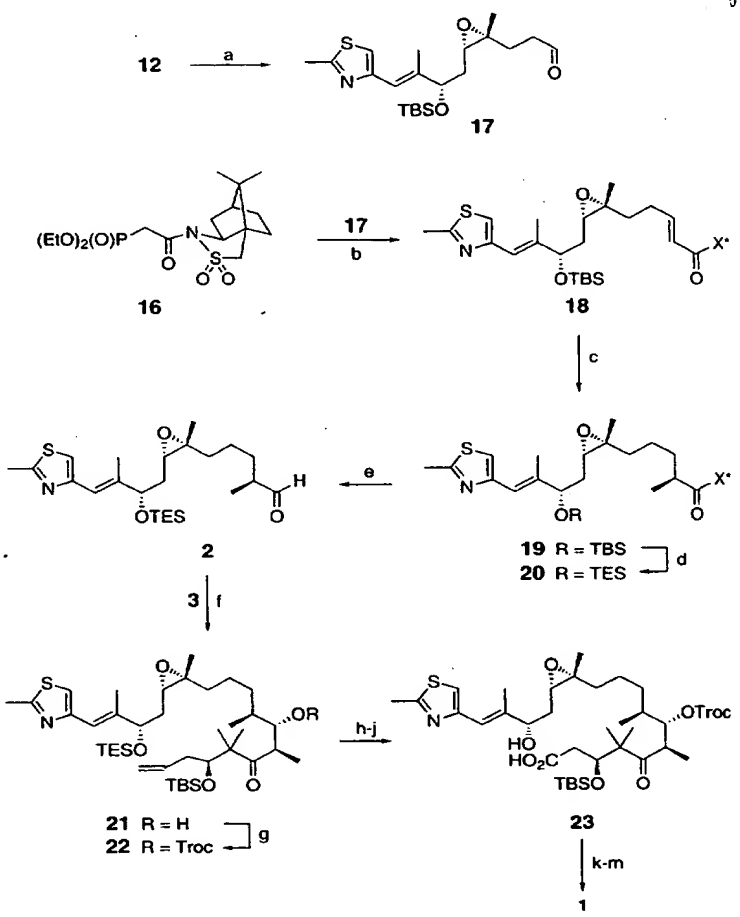
Wittig reaction, the dihydroxylation was much less diastereoselective (3:1). To recover stereochemically misdirected material, **11** was converted into **10** by a double inversion at C12 and C13. Hence, **11** was first converted into the mesylate **13**, which was successively treated with potassium carbonate, water, and 1N HCl (Scheme 3) to give stereoisomerically pure **10** via the nonisolated intermediates **14** and **15**. By this procedure, olefin **4** was converted into the desired (12*R*,13*S*)-epoxide **12** without stereochemical loss. To complete the synthesis of fragment **2**, we used a Horner olefination followed by auxiliary-controlled introduction of the methyl group at C8 (Scheme 4). Thus epoxide **12** was reduced to aldehyde **17**, which was treated with chiral phosphonate **16**[5] in the presence of lithium hydroxide (prepared in situ from BuLi/THF/H_2O) to give the enoylsultam **18** (X* = sulfane residue) in good yield. 1,4-Hydride addition with L-selectride furnished the enolate which was trapped with methyl iodide to give **19** with excellent diastereoselectivity (≥99:1, HPLC analysis).[6] The proper choice of the protective group (PG) for the 15-OH function was particularly important as this PG had to be stable through all transformations up to the macrolactonization. On the other hand, the PG should be removable in the presence of the epoxide at any stage of the sequence. This requirement was extremely hard to fulfil in view of the imminent formation of a 15,12-oxolane ring. A TBS protective group proved insufficient in this respect as its removal proceeded only with 40% yield. However, after conversion of the 15-OTBS derivative **19** into the 15-OTES analogue **20**, all remaining synthetic steps could be carried out in high yield. Specifically, the reductive removal of the auxiliary with DIBAL furnished aldehyde **2** which was treated with the lithium enolate of ketone **3** to give the aldol adduct **21** with a diastereoselectivity of >95:5 (NMR and HPLC analysis). Troc-protection of the 7-OH function gave **22**, which was converted into seco acid **23** by oxidation of the terminal olefin to the aldehyde, followed by 15-O-desilylation and Pinnick oxidation of the aldehyde. Yamaguchi macrolactonization of **23** and removal of the Troc protective group and the 3-OTBS protective group furnished diastereomerically pure **1**.

The epoxide, introduced early into the molecule, has proven its stability under the following conditions: 1) reductive (neutral (DIBAL), ionic (selectride), and metallic (Zn)); 2) oxidative (osmium tetroxide/sodium periodate, sodium chlorite); 3) basic (fluoride in aprotic solvents, DMAP, LDA, enolates). In this respect, it is remarkable that carbon and oxygen anions do not open the epoxide, even when they are generated in a 1,5-relationship to the epoxide; 4) electrophilic (acylation with an acyl chloride in the Yamaguchi reaction). Of all reagents applied, only dilute acid has led to (in this case desired) epoxide opening (**15** → **10**). Apart from providing us with the valuable information that epoxides are by no means such highly reactive intermediates as postulated,[7] the early introduction of the epoxide has been of advantage in the overall synthesis of **1**. For instance, the formation of thiazole-N-oxides previously observed in the *m*-chloroperoxybenzoic acid epoxidation of the C12–C13 double bond[8] has been avoided as well as the formation of the (12*S*,13*R*)-epoxide which is hard to separate from the correct



Scheme 4. Synthesis of epothilone B (**1**) by aldol addition and macrolactonization: a) 1.1 equiv DIBAL, CH_2Cl_2, −95 to −80°C, 1 h, 93%; b) 1.1 equiv BuLi, Et_2O, 0°C, 1.1 equiv H_2O (in THF), then **16**, 5 min, room temperature, then **17**, 30 min, room temperature, 92%; c) 1.4 equiv L-selectride, THF, −78 to −60°C, 0.5 h, 8 equiv HMPA, 12 equiv MeI, −78 to 20°C, 16 h, 78%; d) 1.) 4 equiv TBAF, THF, room temperature, 3 h; 2.) TESCl, NEt_3, cat. DMAP, room temperature, 1 h, 85% over 2 steps; e) 2 equiv DIBAL, CH_2Cl_2, −95 to −80°C, 1 h, 93%; f) 1.5 equiv LDA, 1.5 equiv **3**, −78 to −40°C, −78°C then **2**, 15 min, 92%, diastereoselectivity 95:5; g) 6 equiv 2,2,2-trichloroethoxy chloroformiate (TrocCl), 18 equiv pyridine, CH_2Cl_2, 20°C, 0.5 h, 94%; h) 1.) 0.05 equiv OsO_4, 1 equiv NMO, THF/*t*BuOH/H_2O (5:5:1), room temperature, 16 h; 2.) 3 equiv $NaIO_4$, EtOH/H_2O (4:1), 22°C, 1 h; i) HF·pyridine, pyridine, THF, room temperature, 0.5 h; j) $NaClO_2$, NaH_2PO_4, *t*BuOH/2,2-dimethyl-2-butene (2:1), room temperature, 1 h, 63% for four steps; k) 2.0 equiv 2,4,6-trichlorobenzoyl chloride, 2.5 equiv NEt_3, room temperature, 1 h, then added slowly (1 h) to a solution of 8 equiv DMAP in toluene (0.002 M in seco acid), 0.5 h room temperature, 65%; l) 80 equiv Zn, 100 equiv NH_4Cl, 80°C, 20 min; m) HF·pyridine, pyridine, 30°C, 7 d, 62% for 2 steps. L-Selectride = lithium-tri-*sec*-butylboranate; HMPA = hexamethyl phosphoric acid triamide; TBAF = tetrabutylammonium fluoride; TES = triethylsilyl; DMAP = *N*,*N*-dimethyl-4-aminopyridine; LDA = lithium diisopropylamide; NMO = *N*-methylmorpholine-*N*-oxide.

stereoisomer. Additionally, the diastereocontrol of the aldol addition with the epoxyaldehyde is significantly better than it is with the olefinic aldehyde.[3b,f,g] The use of ester **4** as an intermediate allows the application of the Claisen rearrangement as an efficient chain-elongation procedure. Also, it is possible to introduce additional double bonds after the epoxide has been generated which may be useful for the

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preparation of novel epothilone derivatives. On the other hand, the necessary exchange of the 15-O-silyl protective groups is a clear disadvantage. As to the biological role of the epoxide in epothilone B (**1**), it appears doubtful that it is opened under physiological conditions because of the high stability of the oxirane. Rather, the epoxide may interact with the receptor unchanged or may be used in an intramolecular hydrogen bridge with the 3-OH function to generate a favorable conformation.[9]

Received: April 27, 1999 [Z13320]

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Identification of Toxic 2,4-Decadienal in Oxidized, Low-Density Lipoprotein by Solid-Phase Microextraction

Dieter Spiteller* and Gerhard Spiteller

9-Hydroxy-10,12-octadecadienoic acid (9-HODE) induces the liberation of interleukin-1β (IL-1β) together with α,β-unsaturated aldehydes, especially 2,4-decadienal, from macrophages.[1] IL-1β in turn stimulates the proliferation of smooth muscle cells.[2, 3] This process is regarded as being connected to atherogenesis,[1] since particularly high levels of IL-1β were detected in atherosclerotic plaques.[4] 2,4-Decadienal was detectable only in trace quantities after copper(II) ion induced air oxidation of low-density lipoprotein (LDL).[1] In addition, this detection required long separation procedures and preparation of the 2,4-dinitrophenylhydrazone derivative.[1, 5]

A detection method which needs neither sample procession nor derivatization is solid-phase microextraction (SPME).[6, 7] It also avoids the formation of artifacts by handling. Electron impact mass spectrometry (EI-MS) is excellent for the characterization of α,β-unsaturated aldehydes. We used the combination of SPME/EI-MS to obtain insight into the events proceeding in the artificial oxidation of LDL: Blood samples were withdrawn from volunteers and LDL was isolated immediately.[9] The LDL thus obtained was oxidized by air after addition of catalytic amounts of $CuSO_4$. Samples were collected in time intervals and analyzed by GC/MS. The measurement of the compounds present is achieved by determining the total ion current. Such a chromatogram is reproduced in Figure 1.

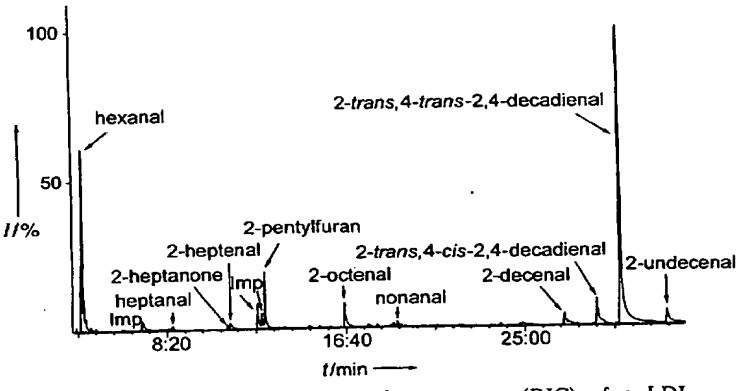

Figure 1. Reconstituted ion current chromatogram (RIC) of a LDL sample after 24 h oxidation with 50 μM $CuSO_4$ solution at 37 °C.

LDL contains different amounts of individual antioxidants which are consumed first. Therefore, some time (lag-time) is required before lipid peroxidation starts.[10] This lag-time also

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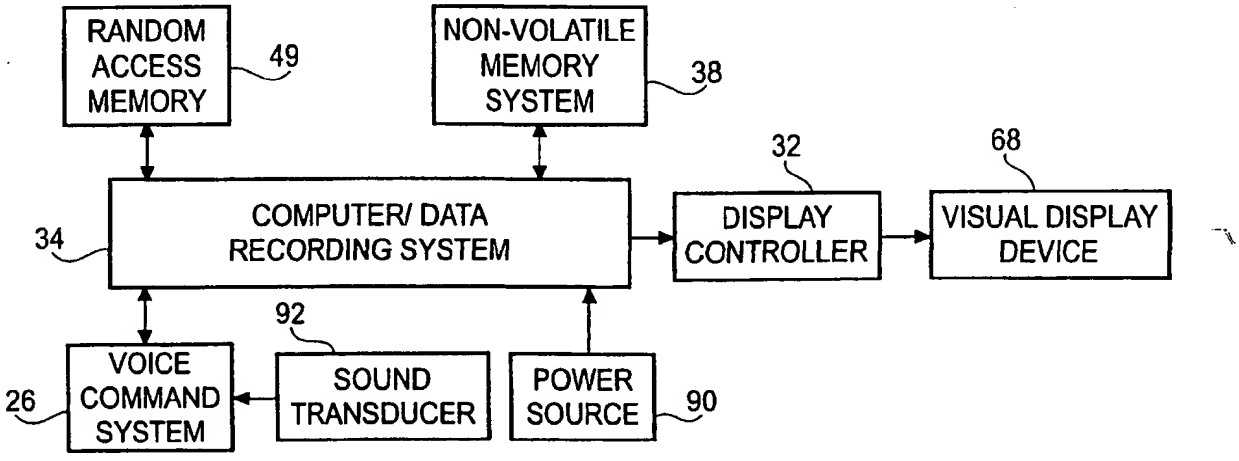

(57) Abstract: An underwater diving mask for use by a diver in an underwater diving environment has a viewing portion defined by the diver's face and a lens, a visual display device proximate the viewing portion to provide visual images to the diver, a speaking chamber configured to sealing engage a portion of the diver's mouth to permit the diver to speak, and a sound transducer located proximal the speaking chamber. A computer system is disposed in a portion of the mask and is operatively coupled to the sound transducer and to the visual display device, where the computer system, the viewing portion and the speaking chamber are sealing isolated from the underwater diving environment. The computer system receives electrical signals produced by the sound transducer and is configured to recognize and identify the electrical signals as spoken words of the diver, such that the identified spoken words provide input to the computer to direct the computer system to provide visual images to the visual display in response thereto, to facilitate hands-free operation of the diver.

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DIVING MASK WITH EMBEDDED COMPUTER SYSTEM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority from co-pending United States provisional application number 60/213,824, filed June 23, 2000, which is commonly owned and incorporated by reference herein.

BACKGROUND OF THE INVENTION

In this written description, the use of the disjunctive is intended to include the conjunctive. The use of definite or indefinite articles is not intended to indicate cardinality. In particular, a reference to "the" object or thing or "an" objection or "a" thing is intended to also describe a plurality of such objects or things.

This invention generally relates to diving equipment and more particularly to a diving mask having an embedded computer system therein.

Some limited purpose underwater "dive" computers inform the diver as to the time remaining before he must surface. While a variety of specialized, non-computerized equipment exists for accomplishing tasks under water, such tasks including communications, lighting, photography, location and direction sensing, homing devices, etc., these devices, in general, have not evolved to the point of having limited purpose computers associated with them.

Although some efforts have been made to modify existing computer hardware for submersed use, such as the WETPC developed by the Marine Institute of Australia, many challenges remain in refining this technology. Adapting computers for use underwater is complicated by the peculiar packaging and ergonomic needs that are inherent in submersing the human body in water.

Foremost, a submersed human must be concerned with life support systems and maintaining spatial awareness. These primary requirements are supported by a variety of specialized devices that assist the submersed human in seeing, breathing, and achieving propulsion through water. To a large degree, the attention of the diver is directed to utilizing or monitoring the various apparatus he has selected to support that primary requirement.

Underwater support equipment, by its nature, is cumbersome and alien. Attaching yet another piece of equipment, such as a computer adapted from the more traditional hardware configurations, is just one more device that must be mounted, cabled, wired, and secured to the diver. This increases drag and provides another point for snagging or malfunction due to

snagging. Such devices are typically mounted or strapped to the diver's arms, legs, torso, or mounted on the air tanks.

Modern conventional desktop personal computer systems are typically used in a dry, indoor area, and consist of a relatively large electronics cabinet, a separate CRT or LCD monitor, a keyboard and mouse. The desktop configuration requires that a user come to the computer because the system is designed as a stationary device. Laptop computers afford the user a certain degree of mobility, but still have restrictions of use due to size, weight, environmental characteristics, and the need for the user to be somewhat stationary while using the computer.

Moreover, most of the current computer hardware technology and applications are directed toward using the computer equipment on land, and do not address the needs of submersed computing. Because 80% of the Earth's surface is covered by water, a skewed ratio of geographical space to computer accessible space exists. The applications for submersed computing and/or underwater data collection are numerous. Demand exists for underwater computer applications in the fields of underwater geography, geology, deep-sea oil exploration, marine biology, construction, excavation, demolition, ship building and maintenance, surveillance, communication, education, and treasure hunting, as well as military uses such as mine clearing and surveillance to name only a few.

Conventionally adapted configurations of computers for body-worn computers require that a head mounted display is placed in front of the diver's eye and tethered to a computer, pressure enclosure, which would typically be mounted on the air tank or elsewhere on the divers body. This would be further tethered to a handheld device (pointing device) used for navigation on the computer screen. One known handheld device is the controller for the Chordic Graphical Interface System developed by the Marine Institute of Australia, which in many ways restricts the range of actual computer applications that can be used while underwater. This is because of its specialized nature and limitations of data input. Additionally, use of hand-held data input devices require the sacrifice of the full use of at least one hand, which may not be practical during a dive because the use of that hand may be required for other activities.

Therefore, the present invention describes a system for underwater computing that combines the specialized equipment needed with standard items of diving equipment, provides enhanced diver streamlining, and allows hands-free user input and control of equipment necessary to a diver.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to diving equipment and more particularly to a diving mask having an embedded computer system therein.

One aspect of this invention is an underwater diving mask for use by a diver in an underwater diving environment. The diving mask has a viewing portion defined by the diver's face and a lens, a visual display device proximate the viewing portion to provide visual images to the diver, a speaking chamber configured to sealing engage a portion of the diver's mouth to permit the diver to speak, and a sound transducer located proximal the speaking chamber. A computer system is disposed in a portion of the mask and operatively coupled to the sound transducer and to the visual display device, where the computer system, the viewing portion and the speaking chamber are sealing isolated from the underwater diving environment. The computer system receives electrical signals produced by the sound transducer and is configured to recognize and identify the electrical signals as spoken words of the diver, such that the identified spoken words provide input to the computer to direct the computer system to provide visual images to the visual display in response thereto, to facilitate hands-free operation of the diver.

In one embodiment of the invention, the diving mask is operatively coupled to the display device such that no wiring or tether external to the diving mask is required.

In another embodiment of the invention, the display device is operatively coupled to the computer system by short length of cabling so that no external cabling extends from the diving mask in a region defined by the diver's head portion to a part of the diver located away from the diver's head.

In a further embodiment of the present invention, the sound transducer is selected from the group consisting of a microphone, crystal microphone, piezoelectric transducer, throat/larynx transducer and vibration transducer, the computer system is selected from the group consisting of a computer, microprocessor, RISC processor, single-chip computer, single-board computer, controller, micro-controller and discrete logic computer, and the display device is selected from the group consisting of a liquid crystal display, LED display, electro-fluorescence display, gas plasma display, prism-type optic display, prismatic projection system and cathode ray tube.

In another embodiment, the present invention further includes non-volatile storage operatively coupled to the computer system, the non-volatile storage is selected from the

group consisting of a ROM, PROM, EPROM, flash memory, optical memory, static memory, bubble memory, memory sticks and hard disk memory.

Still another embodiment includes a speech recognition portion that is configured to receive and process the electrical signals from the sound transducer, and is configured to recognize and identify the electrical signals as the spoken words from the diver, and to provide input to the computer system corresponding to the spoken words.

Yet another embodiment further includes a speech recognition processor operatively coupled to the sound transducer to receive the electrical signals therefrom, and operatively coupled to the computer system, where the speech recognition processor is configured to recognize and identify the electrical signals as the spoken words from the diver and to provide input to the computer system corresponding to the spoken words.

Alternatively, the computer system provides a plurality of predetermined functions displayed on the display device, where the computer system performs at least one of the predetermined functions in response to the input representative of the spoken words of the diver.

In still another embodiment of the invention, the computer system provides one or more menus to the display device, where each menu contains one or more predetermined functions executable by the computer system.

In a still further embodiment, the plurality of menus include a hierarchical set of menus.

In yet another embodiment, the predetermined functions are selected from the group consisting of a menu, pull-down menus, digital camera control applications, life support applications, general purpose applications, gyroscopic/inertial sensor applications, transmitter and receiver applications and power management applications.

Another embodiment includes a gyroscopic/inertial sensor operatively coupled to the computer system.

An alternate embodiment further includes a receiver system operatively coupled to the computer system, which is configured to receive incoming data from the underwater diving environment, and a transmitter system operatively coupled to the computer system and configured to transmit data to the underwater diving environment, where the receiver system and transmitter system are located proximal the diving mask and are sealing isolated from the underwater diving environment.

In another embodiment, the data is selected from the group consisting of speech data, digital data, numerical data and graphical data.

Another aspect of the invention is an underwater diving mask for use by a diver in an underwater diving environment. Such a diving mask has a viewing portion defined by the diver's face and a lens, a display means for providing visual images to the diver, a speaking chamber configured to sealing engage a portion of the diver's mouth to permit the diver to speak, a sound transducer located proximal the speaking chamber, and a computer system disposed in a portion of the mask and operatively coupled to the sound transducer and to the display means. The computer system, the viewing portion and the speaking chamber are sealing isolated from the underwater diving environment. The diving mask has voice recognition means for recognizing and identifying spoken words of the diver, where the identified spoken words are provided to the computer system as input thereto to direct the computer system to provide visual images to the display means in response thereto, to facilitate hands-free operation of the diver.

Alternatively, the voice recognition means is operatively associated with the computer system and is configured to receive the electrical signals from the sound transducer, while the voice recognition means is configured to recognize and identify the electrical signals as the spoken words from the diver and to provide input to the computer system corresponding to the spoken words.

Alternatively, the voice recognition means further includes a voice recognition processor operatively coupled to the computer system and coupled to the sound transducer to receive the electrical signals therefrom, where the speech recognition processor is configured to recognize and identify the electrical signals as the spoken words from the diver and to provide input to the computer system corresponding to the spoken words.

Another still further aspect of the invention is a method of controlling a computer in an underwater diving environment to facilitate hands-free operation of the diver. Such a method includes the steps of:

providing the diver with a diving mask having a viewing portion defined by the diver's face and a lens, placing a visual display device proximate the viewing portion to provide visual images to the diver, incorporating a sound transducer within a speaking chamber, the speaking chamber configured to sealing engage a portion of the diver's mouth to permit the diver to speak, operatively coupling a computer system with the sound transducer and the visual display device, sealingly isolating the computer system, the viewing

portion, and the speaking chamber from the underwater diving environment, speaking into a sound transducer located proximal the speaking chamber to produce electrical signals, receiving and processing the electrical signals by the computer system, the computer system recognizing and identifying the electrical signals as spoken words of the diver, the identified spoken words providing input to the computer, and directing the computer system to provide visual images to the visual display in response to the identified spoken words to facilitate hands-free operation of the diver.

Other features and advantages of the present invention will be apparent to those skilled in the art from the following detailed description, the accompanying drawings and the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The benefits and advantages of the present invention will become more readily apparent to those of ordinary skill in the relevant art after reviewing the following detailed description and accompany drawings:

Figure 1 is a perspective view of a face mask embodying the present invention;

Figure 2 is a front view of a face mask embodying the present invention;

Figure 3 is a side view of a face mask embodying the present invention;

Figure 4 is a block diagram;

Figure 5 is a block diagram of a computer system;

Figure 6 is an elevational view of a prism-type optic that can be swung out of the way of the face plate of a face mask of the present invention;

Figure 7 is a prospective view of an alternate embodiment of the present invention incorporating a display screen;

Figure 8 is a side view of an alternate embodiment of the present invention using a half-silvered mirror in conjunction with a display screen;

Figure 9 is a block diagram;

Figure 10 is a block diagram; and

Figure 11 is a block diagram.

DETAILED DESCRIPTION OF THE INVENTION

While the present invention is susceptible of embodiment in various forms, there is shown in the drawings and will hereinafter be described presently preferred embodiments

with the understanding that the present disclosure is to be considered an exemplification of the invention and is not intended to limit the invention to the specific embodiments illustrated.

It is to be further understood that the title of this section of the specification, namely, "Detailed Description of the Invention" relates to a rule of the United States Patent and Trademark Office, and is not intended to, does not imply, nor should be inferred to limit the subject matter disclosed herein or the scope of the invention.

The invention is comprised of several sub-parts that serve a portion of the total functionality of the invention independently and contribute to system level functionality when combined with other parts of the invention.

A full face mask **10** embodying the present invention is shown in FIGS. 1-3. As will be appreciated by those of ordinary skill in the art, the present invention can also be readily implemented in band masks, full helmets, bubble-type helmets or any other past, present or future construction of a mask or helmet. All of the various embodiments described below can be implemented utilizing all configurations of standard diving masks, or specialized "full face" masks. For example, full face masks suitable for use include the Full Face Mask available from Ocean Reef USA of San Marcos, California, or the balanced regulator Model EXO-BR mask 300-036 or 300-036MS available from Diving Systems International Inc. of Santa Barbara, California. The present invention applies to helmets as well as masks.

Referring to FIGS. 1-3, and FIG. 1 in particular, the illustrated embodiment of the diving masks includes a lens and an oral-nasal portion. The manufacture and design of diving mask lenses is well known in the art and the present invention is not limited to a particular design of lens. The mask is configured so that the mask sealingly engages a diver's eye region to maintain a seal to prevent water from entering the mask. The mask is configured to provide the lens in front of the diver's eyes when the mask is worn. The area between the diver's face and the lens may be considered to be a viewing area because it is this portion through which the diver views the external environment. The external environment or underwater diving environment is any body of water.

The mask is configured such that a speaking chamber is present proximate the diver's mouth to receive sound signals. In one embodiment, the speaking chamber is an open oral-nasal portion configured to sealingly engaging an area about the nose and mouth of the diver. To facilitate speech, the oral-nasal portion defines a cavity around the mouth of the diver to permit speech. As will be appreciated by those of ordinary skill in the art, the oral-nasal

portion is configured to be connected to an air supply, typically from a compressed air tank worn on the diver's back.

The mask is configured to engage the head of the diver. The mask preferably includes a chin strap or an "over the head" strap, or both. In addition to the "off-the-shelf" portions of a diving mask, the mask includes one or more waterproof compartments that contain and protect electronic equipment from water when the mask is submersed. The compartments can be integrally formed with the mask, or can be of modular construction such that the compartments can be attached or detached from the mask as desired. The compartments are waterproof enclosures or cavities sealed along the bridge or sides of the mask, as is known in the art.

The mask of the embodiment illustrated in FIGS. 1-3 may include a first compartment **12** proximate the right ear of the diver, a second compartment **14** proximate the upper right side of the diver's head, a third compartment **16** configured to lie over the diver's head, a fourth compartment **18** adjacent to the upper left side of the diver's head, a fifth compartment **20** proximate to the right ear of the diver, and a sixth compartment **22** located by the right cheek of the diver. However, the present invention is not limited to the above-described number of compartments, and may have fewer than or more than the number described or illustrated, depending upon the diver's needs and the specific underwater application in which the diver is engaged.

Referring now to FIGS. 1-4, the first compartment **12** may contain a peripheral device interface **24**, a voice command (or speech recognition) system **26**, a voice/data receiver **28**, and an interface for a tactile diver input system **30**. The second compartment **14** may have a display controller **32**. The third compartment **16** may include a general purpose computer **34** (synonymous with "computer system" or "computer"), a data encoder/decoder **36**, and a non-volatile memory system **38**. The fourth compartment **18** may have a gyroscopic/inertial sensor **40**, and the fifth compartment **20** may include a voice/data transmitter **42**, a power source interface **44**, and a life support monitoring system **46**. The sixth compartment **22** may include an earphone system **48**. As will be appreciated by those of ordinary skill, the number of compartments can vary, as can the location of particular sub-systems.

Referring to FIGS. 1-4, the diving mask **10** has a fully-functional and self-contained computer system **34** that is contained entirely within the confines of a commercially-available or modified diving mask or full face mask. In defining "contained entirely" or "embedded" it will be understood by those skilled in the art that the computer **34** is effectively incorporated

in the mask **10**, but may be part of a removable module, circuit board, or otherwise be insertable and removable for repair, replacement, configuration or other purposes. At least one watertight sealable compartment is provided to house the computer system **34**. The computer system can be a general purpose computer **34**, preferably located in the third compartment **16** of the mask **10**. As will be appreciated by those of ordinary skill in the art, a general purpose computer system **34** can be constructed in a large number of ways and from a wide variety of available parts. The computer **34** may include a computer, microprocessor, RISC processor, single-chip computer, single-board computer, micro-controller or discrete logic computer (not shown). The computer **34** may have various specialized or general functions implemented as either hardware, software, or firmware. For example, the computer system **34** may contain a speech recognition portion, which may be implemented as hardware, software, or firmware, as described in greater detail hereinafter.

In one preferable embodiment, the computer system **34** is built around a highly-integrated single chip, such as the ZFX86 PC-on-a-chip (Model SOC-MZP-Q-01) available or from ZF Micro Devices, Palo Alto, California. The ZFX86 has several advantages, including high reliability, low power consumption and low heat generation. By providing random-access memory **49** to run the various programs, and optional peripherals as desired, a fully-functional general purpose computer can be constructed. The ZFX86 PC-on-a-chip has an integrated SDRAM controller, thus SDRAM is preferably included as the main memory for use with the ZFX86. Additionally, ZFX86 is energy-efficient, as it draws less than 2 watts of power.

The computer system **34** may further include non-volatile memory **38**. Suitable non-volatile memory devices include, for example, read-only storage, mass storage devices, electronically programmable storage, ROM memory, PROM memory, EPROM memory, EEPROM memory, flash memory, optical memory, static memory, bubble memory and hard disk memory. Some suitable commercially-available products include MICRODRIVE manufactured by IBM Corporation, DISKONCHIP single-disk flash chip, FFD fast flash disk manufactured by M-Systems of Newark, California, FlashDrive manufactured by Sandisk Corporation of Sunnyvale, California, and MEDIASTIK flash modules manufactured by Nexflash Technologies, Inc. of Santa Clara, California. Any suitable commercially available non-volatile storage device may be used, and may be installed as part of the computer system.

Appropriate mounting hardware can be provided to permit the volatile and non-volatile memory to be easily swapped, such as a docking port or socket. For example, a CF+

interface can be provided to permit the MICRODRIVE device to be easily removed and replaced. Those of ordinary skill will appreciate the variety of possible storage media and installation available. Accordingly, any suitable storage system and their equivalents are contemplated by the invention.

Referring to FIG. 5, in an alternate embodiment, the computer system **34** can also be implemented using a variety of separate or discrete chips (including, but not limited to: CPU **50** chips, RAM chips **52**, boot ROM **54**, display memory **56**, disk controller **58**, parallel/serial port controllers **60**, USB controller **62**, bus controllers **64**, cache memory, memory controllers, interface controllers, EIDE device control, timing chips, and the like) mounted on one or more circuit boards in a manner well known to those of ordinary skill in the art.

The computer system **34** may be housed on a printed circuit board assembly designed around a "board on chip" technology, such as that produced, for example, by ZF Microsystems of Palo Alto, California. Alternatively, such printed circuit board assemblies can be any suitable commercial variety, such as, for example, the STRONGARM (SA-1110) boards manufactured by Intel Corporation of Santa Clara, California, the USB CARDPC Model C2I-P5-USB, RAZORBLADE System-On-A-Module Model C2I-RB7-400, or PLUG-N-RUN System-On-A-Module Model C2I-PR5-166, all built by Cell Computing of Santa Clara, California.

Whether implemented around a highly-integrated chip or chip-set, or implemented from a greater number of parts, the computer system **34** is preferably fixedly integrated into the diving mask or helmet **10** in a water-tight manner to protect the computer system from water during diving. Alternatively, the computer system **34** can be placed in a removable module that can be separated from the diving mask and reattached as needed.

The present invention includes a display system **66** that can be implemented in a variety of ways. For example, the display **68** of the present invention can be positioned inside or outside the lens **70**, before either or both eyes, or level with, above or below the eye level.

In the illustrated embodiment of FIGS. 1-3, the display system **66** is an embedded prismatic projection system. The embedded prismatic projection system has a small prism-type optic **72** attached to or manufactured as part of the lens **70** of the face mask **10**. An illuminated image source **74** is placed at the edge of the lens, and projects into the prism-type optic **72**. The diver then views the information from the image source **74** superimposed onto

the lens **70**. This is similar to a "head-up" display system with respect to the image that the user views.

In another specific embodiment, illustrated in FIG. 6, a prism-type optic **72** or prismatic projection system is provided as a modular assembly **76**. The prismatic modular assembly has a prism-type optic **72** and an image source **74**. As illustrated in FIG. 6, the prismatic modular assembly is mounted on a mechanical swivel **78** on the side of the diving mask **10**, which permits the diver to remove the module from the field of vision when it is not required. However, the swivel **78** can be mounted on the top, bottom, or sides of the diving mask **10** as well. Prismatic projections systems developed by MicroOptical Corporation of Boston, Massachusetts, for example, Model Nos. Model EG-7, CO-3 and CO-1 are suitable for use in the present invention.

In yet another embodiment, illustrated in FIG. 7, a display module **80** is attached to the outside of the mask. The module has a self-illuminating image source **82**. Suitable self-illuminating images sources include, but are not limited to, cathode ray tubes (CRT), gas plasma displays, electro-fluorescence display, LED displays, and liquid crystal displays (LCDs).

As illustrated, the external display module **80** can be hinged on a snap-type hinge **84** that is movable into and out of view as desired by the diver. Optionally, the display module **80** may be affixed to the dominant eye side of the diving mask **10**. The self-illuminating image source **82** may further include a power source, such as a battery.

As illustrated in FIG. 8, the self-illuminating display module **80** can be mounted on the top of the diving mask **10** and may use a "Murty" style beam splitter configuration so that the diver views the image by glancing up at a half-silvered mirror **86** that slightly overhangs the mask. The image source **82**, such as a cathode ray tube, gas plasma display or liquid crystal display is positioned out of the field of view of the diver. The half-silvered mirror **86** depends downwardly from the image source and is positioned in the field of view of the diver. Optionally, the half-silvered mirror **86** may be positioned in front of and above a selected dominant eye of the diver. The result is that the image is superimposed over the diver's view of the external environment.

In yet another alternate embodiment, a sealed display (not shown) may be connected partially inside the mask. The mask is constructed to space the front of the mask from the head or face of the diver, such as is common with helmets. A hole may be either pre-formed or drilled in the mask lens to receive a sealed display cylinder (not shown). A prism is

positioned at the end of the cylinder near the eye of the diver. The sealed display includes a monitor, which serves as an image source. A relay lens is positioned to focus the image from the monitor onto the prism, which redirects the image from the monitor to be viewed by the diver. The entire assembly is pressure sealed.

Referring back to FIG. 4, the display controller **32** operably connects the visual display device (or display) **68** to the computer system **34**. As will be understood by those of ordinary skill, selection of the display controller **32** depends on the type of display **68** used. In the prism-type optical display devices discussed earlier, MicroOptics Corporation of Boston, Massachusetts provides suitable display controllers that accept VGA input, such as the Model EG-7, CO-3 and CO-1. When using such prism-type optic displays, the general purpose computer **34** may be provided with a chipset (RAMDAC, video controller, display memory, boot ROM and bus interface) for implementing VGA output, such that the VGA output from the general purpose computer **34** is used as input for the prism-type optical display controller **32**.

In such an embodiment, the prism-type optical display controller **32** is housed and sealed within a specially formed compartment within the diving mask **10**, such as in the second compartment **14** illustrated in FIGS. 1-3. Depending on the display technology selected, a sealed water proof cable may be used to connect to the display **68** with the computer system **34**. The display **68** is operatively coupled to the computer system **34** by a short length of cable **88**. Accordingly, no cable or wire extends from the diving mask in a region defined by the diver's head, to a part of the diver located away from the diver's head, such as the torso, arms, or legs. This reduces or eliminates the possibility of snagging the cable. Alternatively, the cable **88** may be routed through a channel that is molded into the diving mask itself **34**. Preferably, the compartment housing the display controller **32** within the mask is located adjacent to the display **68** to permit the cable or wire connection to the display **68** to be an integral part of the mask **34**, rather than a separate external cable. Accordingly, the computer system **34** may be operatively coupled to the display **68** such that no wiring, cable, or tether extending to the diving mask **10** is required. In the specific embodiments illustrated in FIGS. 1-3 and 5-7, the display controller **32** is located in the second compartment **14**, adjacent to the upper right side of the diver's head. As will be appreciated by those of ordinary skill, if the display **68** is placed on the left hand side, the display controller **32** would preferably also be located on the left hand side, for example, in the fourth compartment **18**.

With respect to a specific example or a suitable display **68**, LCD displays can be controlled via a number of different display controller chips depending on whether a character-based or graphical display is desired. For example, the Hitachi Model 44780 controller may be used with character-based displays while the Toshiba Model T6963C controller may be used with graphical displays. It will be apparent to those of ordinary skill that integrating such chips with a general purpose computer **34** is a straightforward task, which will not be detailed here. Generally, LCD displays draw power directly from the same power source **90** as the general purpose computer **34**. However, the present invention also contemplates displays **68** that draw power from power supplies independent from those of the general purpose computer **34**. Such independent power source, such as batteries, may be housed in a separate compartment.

Referring back to FIG. 4, a sound transducer **92** provides an electrical output signal to the voice command system **26**. Preferably, a microphone **92** installed within the speaking chamber **94** of the full face mask **10** provides the electrical output signal to the voice command system **26**. One example of a suitable microphone and speaking chamber combination is DIVELINK available from Stone Electronics Ltd. of Victoria B.C., Canada and sold as part numbers COMFFR2000-120 (for the OCEAN FREE full face mask) or COMFFA2000-120 (For INTERSPIRO full face masks). Embodiments of the present invention utilizing full diving helmets or the equivalent can have a dedicated microphone located within the helmet. As an alternative to the microphone **92**, the transducer from an artificial larynx can be applied to the throat of a diver. Any suitable sound or vibration transducer may be used. For example, crystal microphones, piezoelectric transducers, and vibration transducers may be used. The sound transducer **92** is preferably located in the speaking chamber **94**, but need not be specifically housed internal thereto. Any suitable location will suffice as long as the sound transducer **92** can receive the voice signals. The voice command system **26** may be the primary user input control device to the general purpose computer **34**, which is housed in the mask **10**. The voice command system **26**, preferably located in the first compartment **12**, accepts the spoken commands of the diver and produces digital signals, which are accepted by the general purpose computer **34**. A speech recognition portion can be included in the voice command system **34** to recognize and identify the electrical signals as spoken words. While the computer **34** and interface to the computer may simultaneously allow connectivity for other user input devices, the voice recognition system eliminates the need for other diver input devices, such as a keyboard,

mouse pointer, and the like, and permits implementation a fully self-contained and streamlined submersible computing system. In this embodiment, the attention of the diver is not diverted, as the diver can focus full attention to the underwater tasks without directing his attention to operation or control of external input devices.

In FIG. 4, one specific embodiment includes a voice activation circuit **96** and a voice recognition system (voice command system) **26**. The voice activation circuit **96** can control whether the general purpose computer **34** is active (fully powered) or in sleep mode (reduced or no power). The voice activation circuit **96** may be a "transitional activator" that brings the computer **34** and peripheral devices from a low-power "sleep" mode to full power. This function may be performed by the voice activation circuit **96** by continuously polling or by use of a pre-determined key word or sound. However, embodiments that rely on the computer **34** for continuous health and safety monitoring do not utilize the power-down embodiment.

In another specific embodiment, the speech recognition system **26** and voice activation circuit **96** are included in a speech recognition processor such as the RSC-300/364 devices produced by Sensory Inc. of Palo Alto, California. Preferably, the RSC-300 is used. The RSC-300 can be programmed to operate in a low power continuous listening mode until a particular digital pattern (digitized sound) is received from the sound transducer **92**. One advantage of the RSC-300/364 devices is that they have automatic gain control to compensate for input that may not be optimal due to the position of the microphone. Another advantage of the RSC-300/364 devices is lower power consumption, drawing only about 10 mA at 3V. The speech recognition system **26** can reside on a computer board in the first compartment **12** or may be located at another location between the sound transducer **92** and the general purpose computer **34**.

The speech recognition system **26** is operatively coupled to the microphone or sound transducer **92** and receives the electrical signals from the sound transducer **92**. The speech recognition system **26** is also operatively coupled to the computer system **34** and is configured to recognize and identify the electrical signals as the spoken words from the diver. The spoken words or input is provided to the computer system **34**, which performs various functions depending upon the spoken words.

In another embodiment, the speech recogntion system **26** includes an amplifier and analog-to-digital conversion devices. Analog-to-digital converters accept input from the microphone **92** and provide suitable digital signals to the general purpose computer **34**. For

example, a "sound card" for a personal computer, such as the Hercules Game Theatre XP Sound Card Model by Guillemot Corp. may be used. In such implementations, the general purpose computer **34** is provided with software to process the voice signals to recognize the command given. Such software may be, for example, Dragon Naturally Speaking Professional voice recognition software by Dragon Systems, Inc. or VIVE VOICE by IBM Computer.

In this embodiment, the computer system **34** includes a speech recognition portion, which first receives the electrical signals from the sound transducer **92**. The electrical signals are converted into digital signals. The speech recognition portion then processes the digital signals so as to recognize and identify the digital signals as the spoken words from the diver. Input is provided to the computer system corresponding to the spoken words so that various actions may be taken.

In general, whether the voice recognition function is provided within the computer system **34** or by a separate voice recognition processor, the end result is the same. When a spoken word is processed, the computer **34** receives input corresponding to that word, which may be a numeric code or ACCII string. For example, if the diver speaks the word "FILE," the computer **34** may display a pull-down menu called "FILE," which may be similar to the FILE menu present in many the Microsoft WINDOWS applications. In summary, the diver, through spoken words and voice recognition, can control the operation of the computer system without using external input devices.

In one embodiment, electrical power for the computer system **34** is provided by a power source **90** located in the diving mask **10**, preferably in a battery pack located above the eye portion of the mask in the third compartment **16**. In an alternate embodiment, power for the computer system **34** is provided by a power supply external to the mask. In this specific embodiment, the power cable is tethered to a diving harness on the diver's shoulder to reduce the risk of the power cable snagging or otherwise encumbering the diver.

A wide variety of suitable power sources **34** exist for powering the electrical components of the present invention. Various types of batteries may be used as power sources **34**, such as nickel-cadmium batteries, lithium ion batteries, and lithium polymer batteries. When available in production quantities, moldable lithium polymer batteries may be used, which can be molded into various shapes for suitable incorporation into the diving mask. Preferably, the batteries are vented using a check valve or other suitable venting

mechanism to allow the safe venting of gasses that may be generated, as is known to those of ordinary skill in the art.

Referring to FIG. 4, the present invention may also include a dive monitoring sensor system **98** embedded within the mask **10** or contained within a sealable compartment. The dive monitoring sensor system **98** includes clock circuitry and memory, which is dedicated to the recording of pressure measurements as a function of time. Further electronics can be linked to the sensors **98** to provide data conventionally provided by traditional dive computers. The dive monitoring sensor system **98** is operatively connected to the computer **34** and provides the computer **34** with sensor data for recording and/or display. Application software in the computer **34** can be configured to record and display data such as depth, dive time, bottom time, decompression limits and tissue nitrogen loading, as is known by one skilled in the art. As shown in FIG. 4, integration of the items above with a low pressure hose connection device **100** from the diver's air supply allows the inclusion of an air gauge display. This integration obviates the need for other types of life support systems or monitoring instrumentation. The reduction of systems and/or instrumentation further streamlines the profile of the diver in the water and minimize distractions from tasks at hand.

Additionally, as shown in FIGS. 1-3, a digital camera **102** can be attached to or molded into the body of the dive mask **10** or full face mask. A digital camera system housing **104** is incorporated above the lens of the mask **10** anterior to the third compartment **16**. The compartments and digital camera system **102** can be formed as a continuous shell that is attached securely to the periphery of the face mask **10**. As illustrated in FIG. 4, the digital camera **102** can be attached to the computer system **34** through appropriate interface electronics, as is known in the art. For example, the ZFX86 processor includes a USB bus allowing USB digital cameras to be installed with minimal effort. A suitable camera module, for example, the C3188 module plus OV511 USB controller, may be used in the present invention, which are available from Quasar Electronics Limited of the United Kingdom. Application software resident in the computer system **34** permits the diver to control the digital camera **102** electronically in a hands-free way via the voice commands. For example, the diver can use the display **68** as a view finder to see the current field of view "seen" by the camera **102**. Accordingly, the image that the camera **102** "sees" is presented to the diver by the display device **68**. Further, the software can be programmed to allow the diver to adjust the field of focus of the camera **102** in the mask-mounted display **68**, or may be directed to capture of a single frame or a stream of video pictures with specific commands. The use of

the computer **34** also allows storage of pictures within the non-volatile memory **38** of the computer **34** (such as memory sticks, flash cards, and the like) dedicated solely to the digital camera.

The mask **10** can also have an underwater earphone device **48**. Earphones for use underwater are typically bone conduction-type earphones. Such earphones are desirable because the diver's outer ear is normally filled with water when diving, which greatly reduces the diver's ability to hear. However, sound signals can be transmitted to the diver by mechanical vibration via the bone around the ear. The sound is then transmitted to the inner ear. While the proper location for the earphone varies somewhat from diver to diver, it will generally be on a bony protrusion of the skull, as is known to one skilled in the art. A speaker may be provided in the helmet-type mask.

In a further embodiment illustrated in FIG. 4, the mask may include a transceiver system **108** having a receiver **110** (or reception system) for receiving incoming transmissions, and a transmitter **112** (or transmission system) for sending outgoing transmissions. Incoming transmissions can either be voice or can be digitally encoded and/or encrypted voice/data transmissions. Data such as speech, numeric data, and graphical data may be transmitted or received. Such data may be analog or digital in nature. Any suitable type of transmission medium may be used, such as, for example, short haul RF, ultrasonic, laser or other means. Transceivers **108** suitable for use with the present invention include The BUDDY PHONE line, Model OR-BUD/S, and Ocean Reef USA, Model GSM, Code 33105, by Ocean Technology Systems and DIVELINK Communicator, COM-U01 by Stone Electronics of Victoria, Canada. The receiver **110** can include a tuner, amplifier, gain control system, and the like, which enables the receiver to select a desired incoming transmission.

Referring to FIG. 4, the voice/data receiver **28** also includes a modem for incoming signals that accept the incoming signal from the receiver **110**. The voice/data transmitter can also include a modem for outgoing signals to be routed to the transmitter **112**. A signal splitter can split the incoming signal so that the signal (if speech) can be heard by the diver via the earphone **48** and can also be processed by the modem, which provides the data to the computer. The design and construction of signal splitters and modems is well known, and any number of commercially available implementations can be used in the present invention. Similarly, the transmitter can receive input from either the computer **34** or the sound transducer **92** so that the transmitter **112** can be used by the computer **34** to transmit data or commands to the diver or to transmit voice messages.

Incoming digital transmissions directed to the computer **34** can be decoded and /or decrypted by software residing on the computer **34**. Alternatively, the received digital transmissions can be decoded and/or decrypted by dedicated hardware such as the data encoder/decoder **36** illustrated in FIG. 4. The computer **34** can then process the decoded and/or decrypted digital information with software and act accordingly, such as by displaying the received data on the display.

In another embodiment, illustrated in FIG. 4, a peripheral device control system **24** is included. The peripheral device control system **24** permits the computer **34** to function as a controlling device for other peripheral devices that may be attached to the diver's body and the computer. Such peripheral devices include various data acquisition devices, scientific instruments, weapons systems, and the like, and can be directed by the diver via means of voice commands as described above. Appropriate underwater interfaces and waterproof cabling can be provided to route the appropriate inputs to the computer. For example, the ZFX86 chip described above is capable of controlling a wide variety of devices including, but not limited to, parallel port devices, serial port devices, USB port devices. Optionally, a BLUETOOTH interface can be provided for the computer for use with short range wireless BLUETOOTH devices as peripherals for the general purpose computer. Further, the diving mask **10** can be provided with electronics for detecting underwater homing devices and providing range and direction information to the computer.

The system can also include a tactile diver input system **30**. A tactile diver input system **30** can be as simple as a switch or button, or can be more complex, such as the Chordic input interface available from WetPC of Australia.

Referring to FIG. 4, the system of the present invention may also includes a gyroscopic / inertial sensor input system **40**. The gyroscopic / inertial sensor **40** is operatively connected to the computer **34**, preferably via the USB bus, and acts as a pointing device. A suitable gyroscopic / inertial sensor **40** is the Microgyro 100 is manufactured by Gyrations Corporation of Saratoga, California. An alternative inertial sensor that operates in three planes is the INTERTRAX2 available from Intersense of Burlington, Massachusetts.

As described above, the diver can input commands to the computer **34** in a hands-free manner by speaking into the sound transducer **92**. The sound transducer **92** translates the diver's speech into electrical signals and passes those signals to the voice command portion **26** or voice recognition processor. The voice command portion **26** then recognizes and identifies the spoken sound or word. The recognized word is then passed to the computer

system **34** to be associated with a command or a selected function shown on the display device **68**.

In one embodiment, the computer **34** is programmed to accept commands via a series of hierarchical menus. For example, the highest level of menu may contain a list of the subsystems controlled by the computer **34**, such as:

1) LIFE SUPPORT SYSTEMS
2) EXTERNAL PERIPHERAL DEVICES
3) CAMERA
4) GYROSCOPIC/INERTIAL SENSOR INPUT
5) RECEIVER
6) TRANSMITTER
7) POWER MANAGEMENT
8) COMPUTER PROGRAM APPLICATIONS

Thus the diver could select life support system monitoring **46** by saying the word "one" or check the power level of his battery by saying the word "seven."

The use of a numbered list is exemplary. A wide variety of methods of displaying menus are known in the art, and are contemplated by the present invention. Alternative mechanisms may include selection by letter index (A, B, C), key word index (LIFE, EXTERNAL, CAMERA, GYRO, RECEIVER, TRANSMITTER, POWER), or by highlighting the current selection and having the diver manage selection by selecting the "next" or "previous" selection. For example, in the menu above, if "LIFE SUPPORT SYSTEM" above was highlighted, by saying "next, next, select" the diver would select the DIGITAL CAMERA SYSTEM menu or application.

As illustrated, the computer system **34** may provide a plurality of predetermined functions or applications, which are displayed on the display device **68**. The computer system **34** is configured to perform at least one of the predetermined functions in response to the input representative of the spoken words of the diver. Each function shown and selected may represent a self-contained task, which can be directly performed by the computer system **34**, or may cause one or more additional menus or sub-menus to be displayed. Each sub-menu may contain additional predetermined functions or additional sub-menus. Accordingly, the menus may be hierarchical sets of menus.

In an alternate embodiment, a vocabulary is developed for control of the computer **34**. A vocabulary can include of a plurality of recognition sets. Each recognition set includes one

or more words. As will be apparent to those of ordinary skill in the art, a recognition set having fewer words provides better performance in a speaker-independent environment. Further, it will be apparent to those of ordinary skill that it is easier to distinguish among a small set of words than a large set of words. Preferably, when using the RSC-300 speech recognition processor or system **26**, each recognition set has no more than fifteen words. Typically, the speech processor **26** will have only one recognition set active at a time. The speech processor **26** monitors the electrical signals generated by the sound transducer **92** to recognize patterns corresponding to words in the limited vocabulary. When the speech processor **26** recognizes a word, it transmits a corresponding word signal to the computer system **34**.

The computer **34** may include various resident application programs, which may correspond to the menu selection described above. Further, the display of the various menus may be a "high-level" application program, and various recognition sets may be associated therewith. The recognition set may change depending upon the application selected. The computer **34** may respond to a word signal by changing the recognition set. For example, when the computer **34** recognizes the spoken word "camera," as shown as selection number three of the eight selections previously described, it programs the speech recognition processor **26** with a recognition set appropriate to the camera control program. The next spoken word may then represent a specific command to be executed, at which point the computer **34** would execute the appropriate command. Thus, in the "camera" speech recognition set, the word "snap" might trigger the taking of a picture. The following are examples of various applications and menu selection, and are exemplary in nature and are not intended to limit the scope of the present invention.

EXAMPLE 1 - Photography

Referring to FIG. 9, a diving mask **10** for underwater photographic work is constructed with the computer **34**, voice command system **26**, sound transducer **92**, digital camera **102**, display controller **32** and display **68**. When the DIGITAL CAMERA option is selected from the main menu illustrated above, a sub-menu for controlling the digital camera **102** displays the following sub-menu:

1) RETURN TO MAIN MENU
2) DISPLAY CURRENT CAMERA VIEW
3) ZOOM FIELD-OF-VIEW OUT
4) ZOOM FIELD-OF-VIEW IN

5) SINGLE SHOT

6) BEGIN VIDEO STREAM

7) END VIDEO STREAM

The menu items are selected by the diver by speaking the number of the menu selection. For example, the diver can then easily command the taking of photographs as needed while keeping his hands free to move a lot or operate equipment.

EXAMPLE 2 - PORTABLE INSTRUCTION MANUAL

Referring to FIG. 10, the computer **34** can be programmed to provide an instruction manual for a task to be performed. For example, the diver may "call up" an instruction manual showing the details of how to repair an underwater cable or pipe. Alternatively, the instruction manual may be in the form of a series of instructional elements or a checklist. The computer **34** may be programmed to move forward or backward among the instructional elements when the speech processor indicates to the computer that the diver has said "next" or "previous. " The diver can thereby navigate a checklist by saying "next" or "previous."

EXAMPLE 3 - DATA COLLECTION

Referring to FIG. 11, the computer **34** can be programmed to present the diver with options for data entry. For example, the computer **34** may implement software such as Dragon Naturally Speaking or Viva Voice software described above to transcribe input spoken by the diver. Alternatively, the computer **34** can simply record digitized signals received from the voice command system **26** as data in the non-volatile memory **38**. Further, the computer **34** can be programmed with application-specific software that prompts the diver for data entry of a specific kind. For example, if the diver is cataloging undersea plants and animals, the computer can timestamp hierarchical menus that enable the diver to enter data regarding the discovery for storage by the computer **34**. The computer **34** can automatically time-stamp the entries to relieve the diver of one kind of mundane aspect of data collection.

From the foregoing it will be observed that numerous modifications and variations can be effectuated without departing from the true spirit and scope of the novel concepts of the present invention. It is to be understood that no limitation with respect to the specific embodiment illustrated is intended or should be inferred. The disclosure is intended to cover by the appended claims all such modifications as fall within the scope of the claims.

CLAIMS

What is claimed is:

1. An underwater diving mask for use by a diver in an underwater diving environment, the diving mask comprising:

a viewing portion defined by the diver's face and a lens;

a visual display device proximate the viewing portion to provide visual images to the diver;

a speaking chamber configured to sealing engage a portion of the diver's mouth to permit the diver to speak;

a sound transducer located proximal the speaking chamber;

a computer system disposed in a portion of the mask and operatively coupled to the sound transducer and to the visual display device;

the computer system, the viewing portion and the speaking chamber sealing isolated from the underwater diving environment; and

the computer system receiving electrical signals produced by the sound transducer and configured to recognize and identify the electrical signals as spoken words of the diver, the identified spoken words providing input to the computer; to direct the computer system to provide visual images to the visual display in response thereto to facilitate hands-free operation of the diver.

2. The diving mask of claim 1 wherein the computer system is operatively coupled to the display device such that no wiring or tether external to the diving mask is required.

3. The diving mask of claim 1 wherein the display device is operatively coupled to the computer system by short length of cabling so that no external cabling extends from the diving mask in a region defined by the diver's head portion to a part of the diver located away from the diver's head.

4. The diving mask of claim 1 wherein

the sound transducer is selected from the group consisting of a microphone, crystal microphone, piezoelectric transducer, throat/larynx transducer and vibration transducer;

the computer system is selected from the group consisting of a computer, microprocessor, RISC processor, single-chip computer, single-board computer, controller, micro-controller and discrete logic computer; and

the display device is selected from the group consisting of a liquid crystal display, LED display, electro-fluorescence display, gas plasma display, prism-type optic display, prismatic projection system and cathode ray tube.

5. The diving mask of claim 1 further including non-volatile storage operatively coupled to the computer system, the non-volatile storage is selected from the group consisting of a ROM, PROM, EPROM, flash memory, optical memory, static memory, bubble memory, memory sticks and hard disk memory.

6. The diving mask of claim 1 wherein the computer system further includes a speech recognition portion configured to receive and process the electrical signals from the sound transducer, and recognize and identify the electrical signals as the spoken words from the diver, and to provide input to the computer system corresponding to the spoken words.

7. The diving mask of claim 1 further including a speech recognition processor operatively coupled to the sound transducer to receive the electrical signals therefrom, and operatively coupled to the computer system, the speech recognition processor configured to recognize and identify the electrical signals as the spoken words from the diver and to provide input to the computer system corresponding to the spoken words.

8. The diving mask of claim 1 wherein the computer system provides a plurality of predetermined functions displayed on the display device, the computer system performing at least one of the predetermined functions in response to the input representative of the spoken words of the diver.

9. The diving mask of claim 1 wherein the computer system provides one or more menus to the display device, each menu containing one or more predetermined functions executable by the computer system.

10. The diving mask of claim 9 wherein the plurality of menus include a hierarchical set of menus.

11. The diving mask of claim 8 wherein the predetermined functions are selected from the group consisting of a menu, pull-down menus, digital camera control applications, life support applications, general purpose applications, gyroscopic/inertial sensor applications, transmitter and receiver applications and power management applications.

12. The diving mask of claim 11 further including a gyroscopic/inertial sensor operatively coupled to the computer system.

13. The diving mask of claim 1 further including

a receiver system operatively coupled to the computer system and configured to receive incoming data from the underwater diving environment;

a transmitter system operatively coupled to the computer system and configured to transmit data to the underwater diving environment; and

the receiver system and transmitter system located proximal the diving mask and sealing isolated from the underwater diving environment.

14. The diving mask of claim 13 wherein the data is selected from the group consisting of speech data, digital data, numerical data and graphical data.

15. An underwater diving mask for use by a diver in an underwater diving environment, the diving mask comprising:

a viewing portion defined by the diver's face and a lens;

a display means for providing visual images to the diver;

a speaking chamber configured to sealing engage a portion of the diver's mouth to permit the diver to speak;

a sound transducer located proximal the speaking chamber;

a computer system disposed in a portion of the mask and operatively coupled to the sound transducer and to the display means;

the computer system, the viewing portion and the speaking chamber sealing isolated from the underwater diving environment;

voice recognition means for recognizing and identifying spoken words of the diver; and

the identified spoken words provided to the computer system as input thereto to direct the computer system to provide visual images to the display means in response thereto to facilitate hands-free operation of the diver.

16. The diving mask of claim 15 wherein the voice recognition means is operatively associated with the computer system and is configured to receive the electrical signals from the sound transducer, the voice recognition means configured to recognize and identify the electrical signals as the spoken words from the diver and to provide input to the computer system corresponding to the spoken words.

17. The diving mask of claim 1 wherein the voice recognition means further includes a voice recognition processor operatively coupled to the computer system and coupled to the sound transducer to receive the electrical signals therefrom, the speech recognition processor configured to recognize and identify the electrical signals as the spoken

words from the diver and to provide input to the computer system corresponding to the spoken words.

18. A method of controlling a computer in an underwater diving environment to facilitate hands-free operation of the diver, the method comprising the steps of:

providing the diver with a diving mask having a viewing portion defined by the diver's face and a lens;

placing a visual display device proximate the viewing portion to provide visual images to the diver;

incorporating a sound transducer within a speaking chamber, the speaking chamber configured to sealing engage a portion of the diver's mouth to permit the diver to speak;

operatively coupling a computer system with the sound transducer and the visual display device;

sealingly isolating the computer system, the viewing portion, and the speaking chamber from the underwater diving environment;

speaking into a sound transducer located proximal the speaking chamber to produce electrical signals;

receiving and processing the electrical signals by the computer system, the computer system recognizing and identifying the electrical signals as spoken words of the diver, the identified spoken words providing input to the computer; and

directing the computer system to provide visual images to the visual display in response to the identified spoken words to facilitate hands-free operation of the diver.

FIG. 1

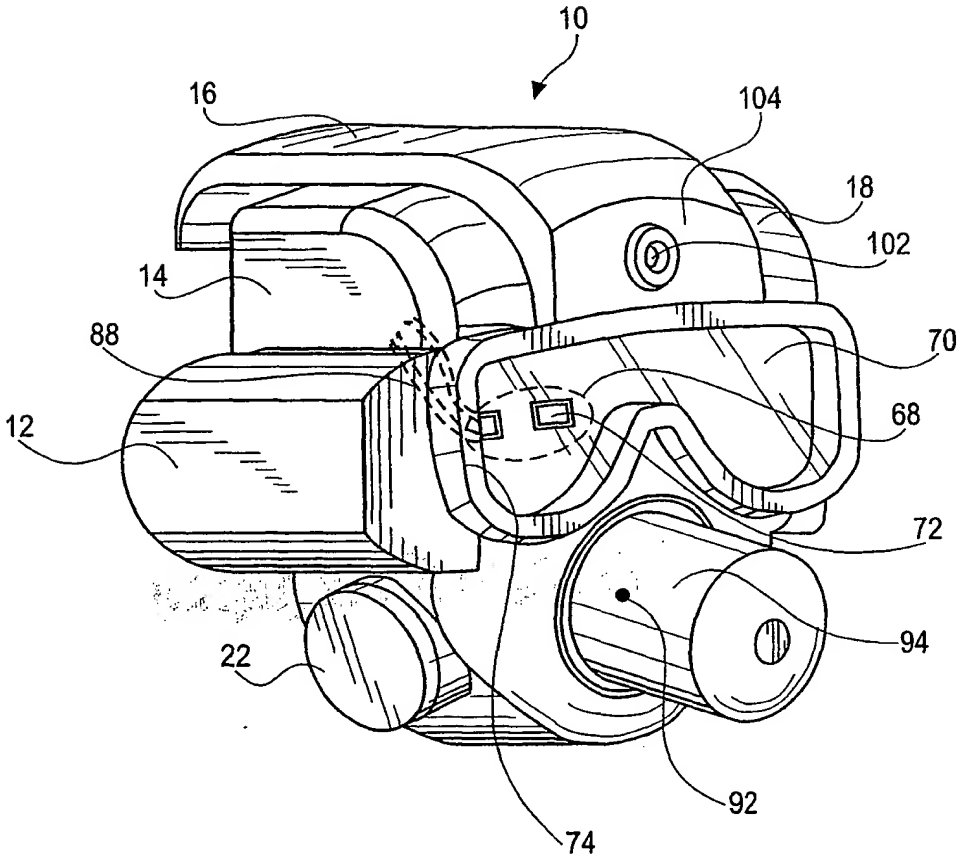


FIG. 2

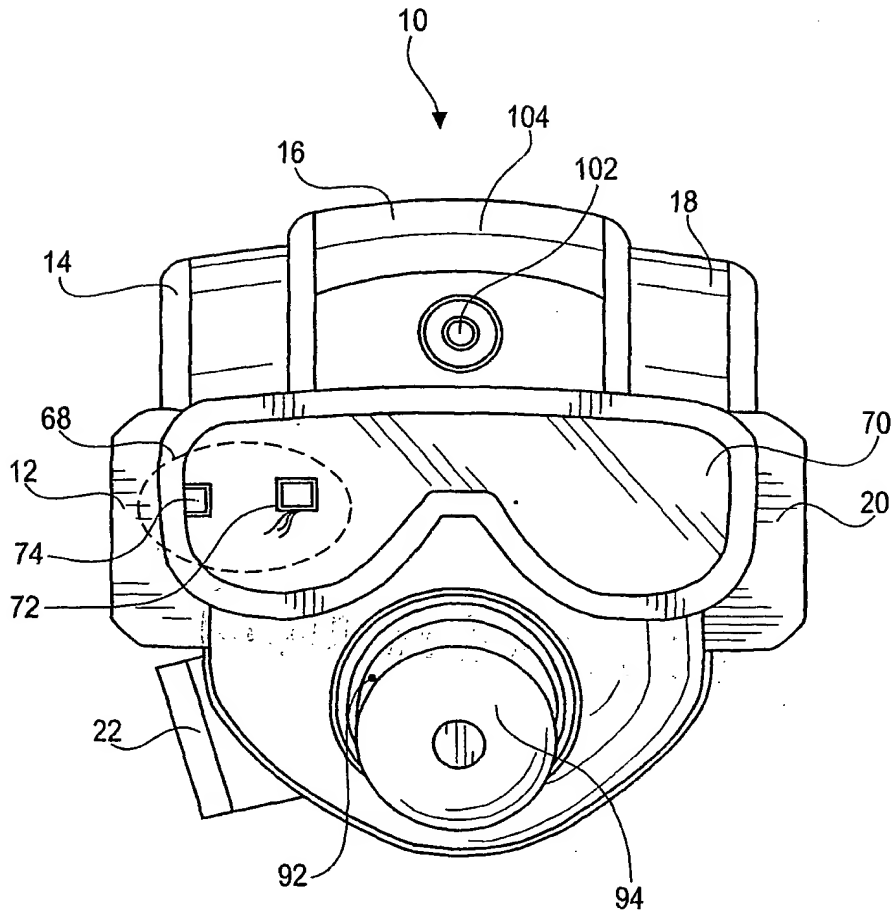
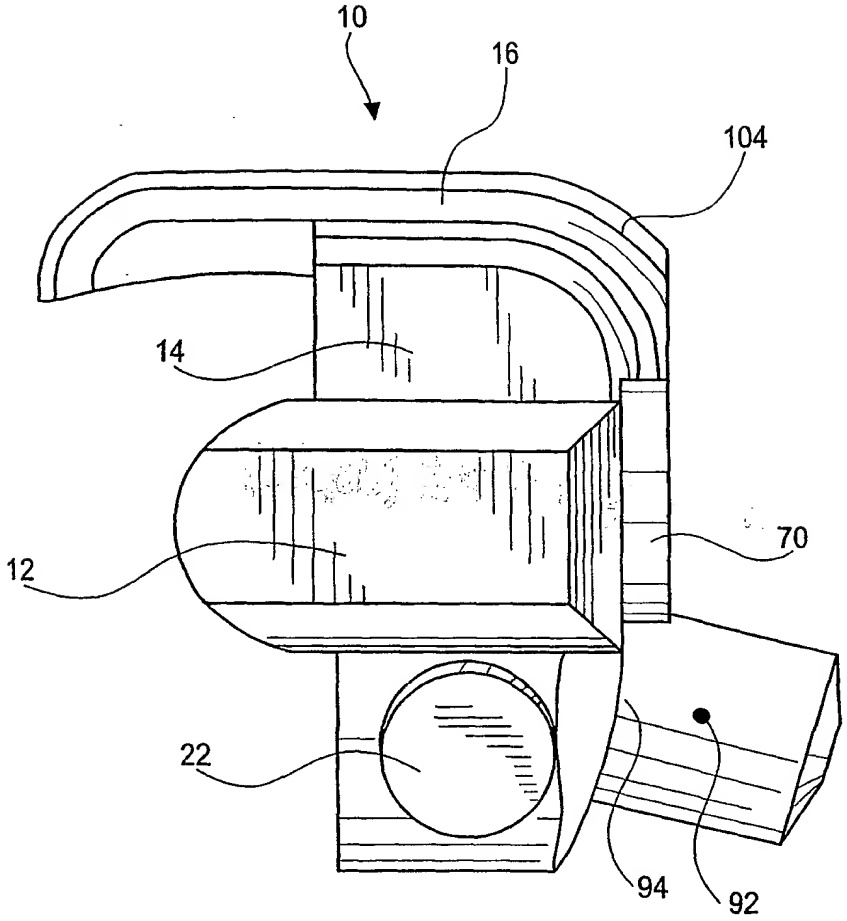
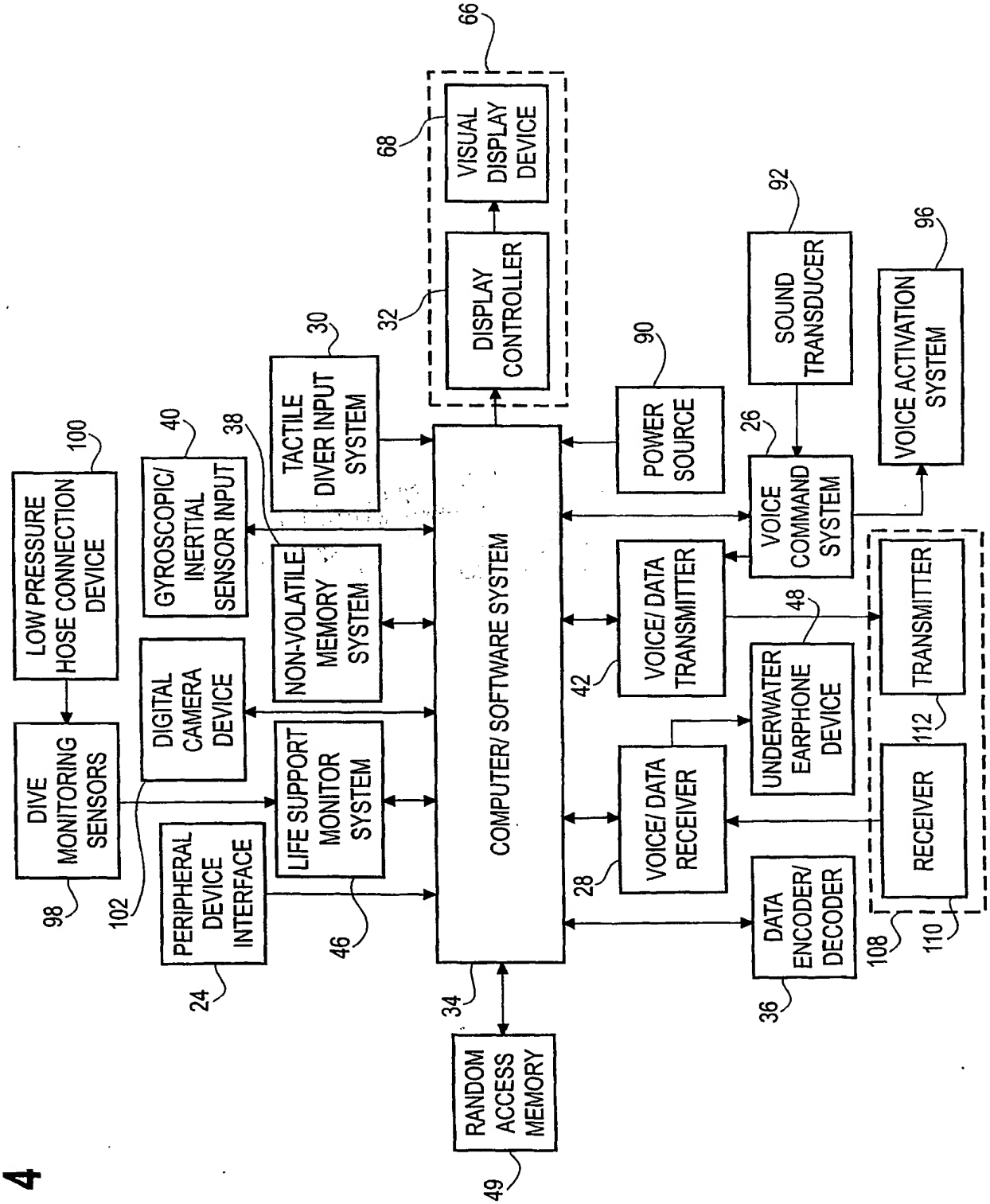


FIG. 3




LOW PRESSURE HOSE CONNECTION DEVICE
100
DIVE MONITORING SENSORS
98
DIGITAL CAMERA DEVICE
102
PERIPHERAL DEVICE INTERFACE
24
GYROSCOPIC/ INERTIAL SENSOR INPUT
40
NON-VOLATILE MEMORY SYSTEM
38
LIFE SUPPORT MONITOR SYSTEM
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TACTILE DIVER INPUT SYSTEM
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COMPUTER/ SOFTWARE SYSTEM
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RANDOM ACCESS MEMORY
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DISPLAY CONTROLLER
32
VISUAL DISPLAY DEVICE
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POWER SOURCE
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VOICE/ DATA TRANSMITTER
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VOICE/ DATA RECEIVER
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DATA ENCODER/ DECODER
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SOUND TRANSDUCER
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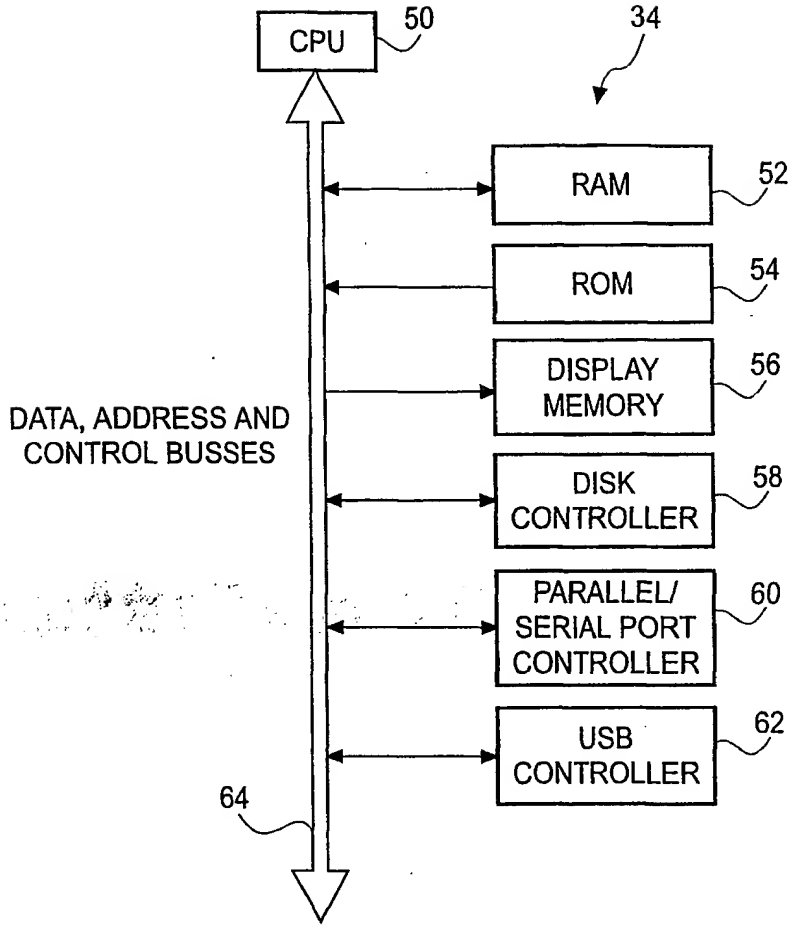
VOICE COMMAND SYSTEM
26
UNDERWATER EARPHONE DEVICE
48
VOICE ACTIVATION SYSTEM
96
TRANSMITTER
112
RECEIVER
108
110

FIG. 4

FIG. 5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PARALLEL/ SERIAL PORT CONTROLLER
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USB CONTROLLER
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DATA, ADDRESS AND CONTROL BUSSES
64

FIG. 6

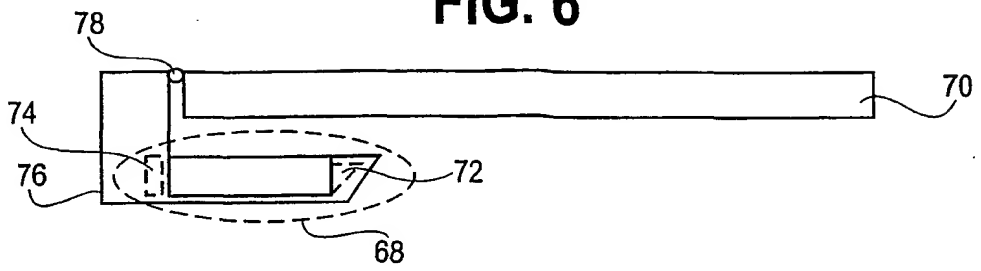


FIG. 7

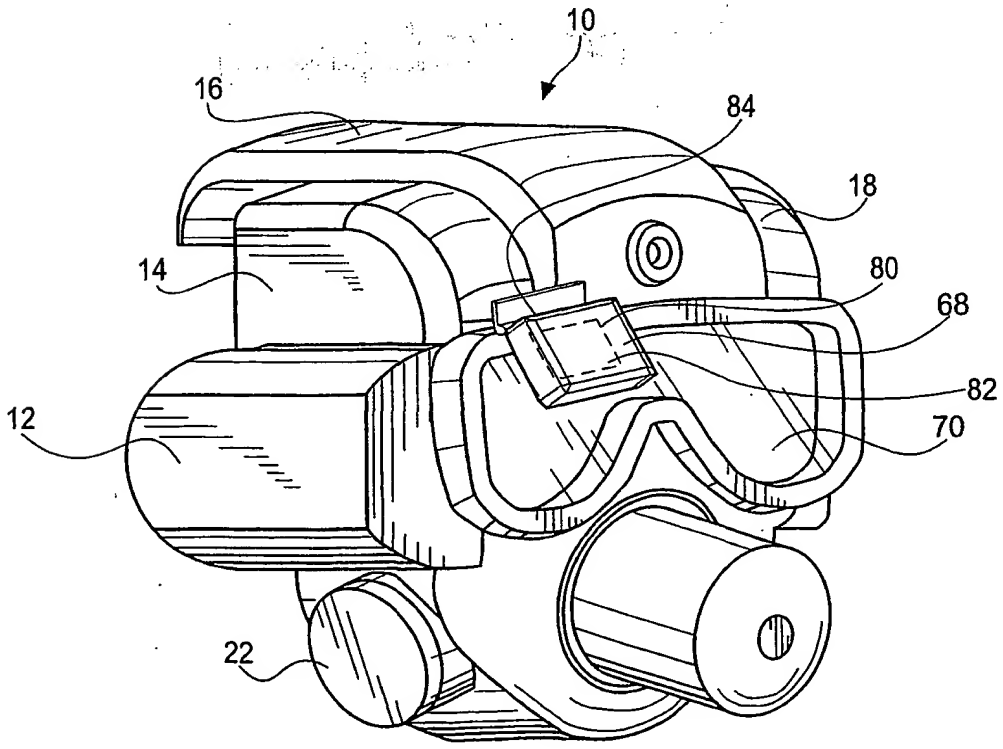


FIG. 8

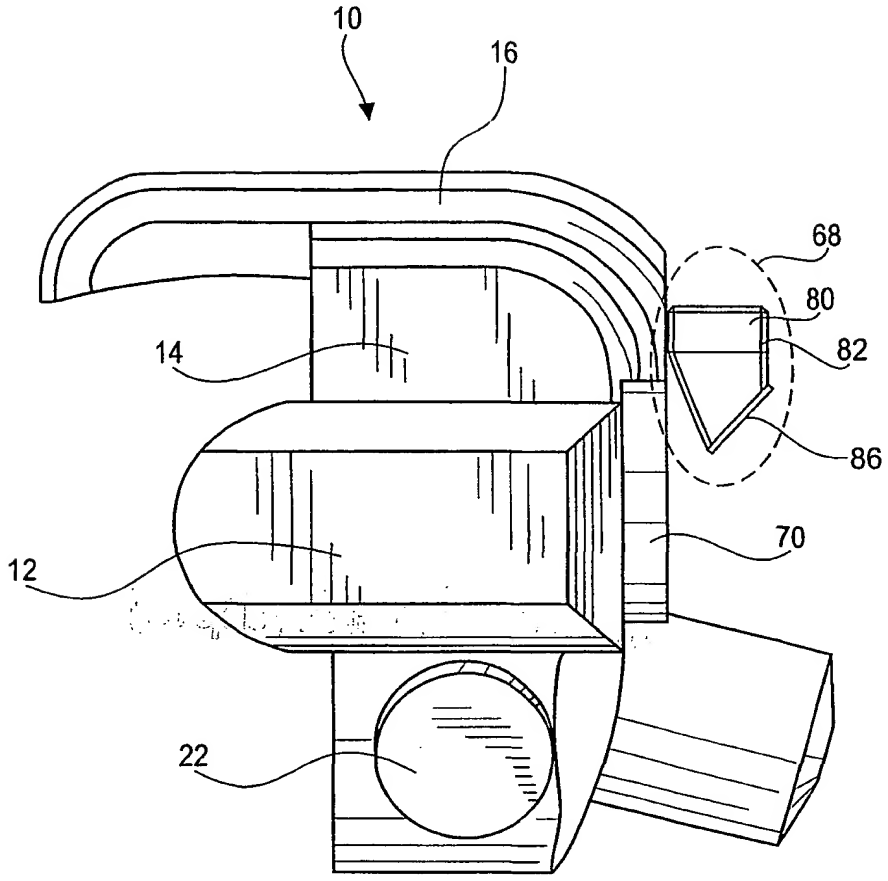
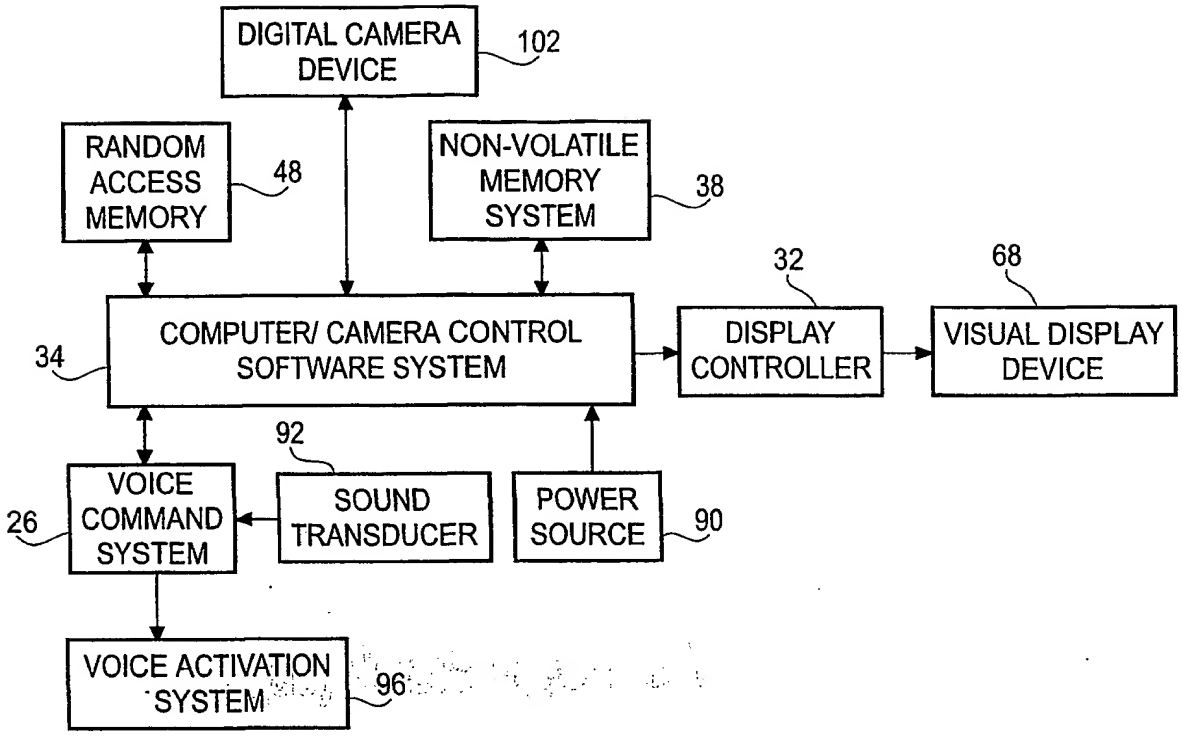


FIG. 9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COMPUTER/ CAMERA CONTROL SOFTWARE SYSTEM
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DISPLAY CONTROLLER
VISUAL DISPLAY DEVICE
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VOICE COMMAND SYSTEM
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SOUND TRANSDUCER
POWER SOURCE
90
VOICE ACTIVATION SYSTEM
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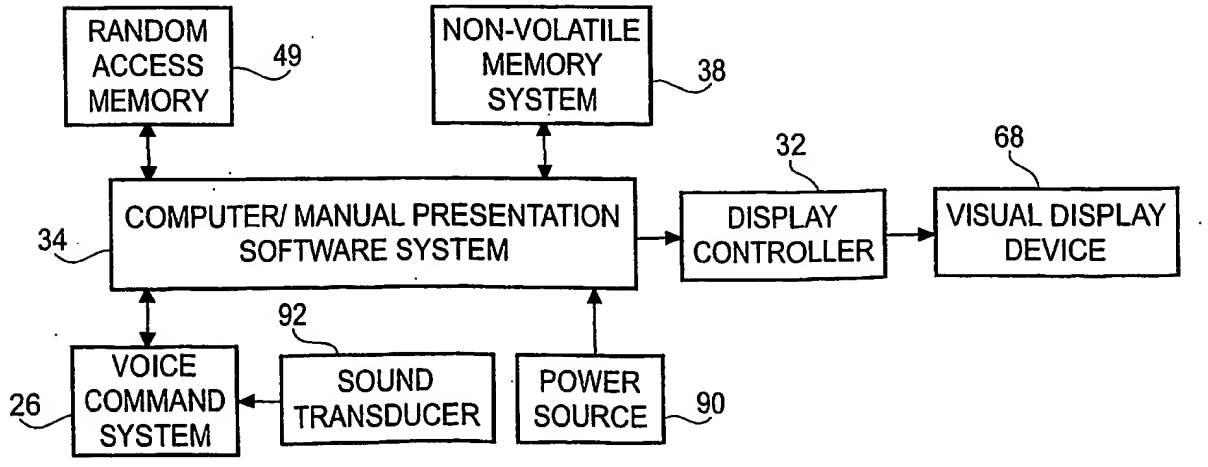
FIG. 10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DISPLAY CONTROLLER
VISUAL DISPLAY DEVICE
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VOICE COMMAND SYSTEM
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SOUND TRANSDUCER
POWER SOURCE
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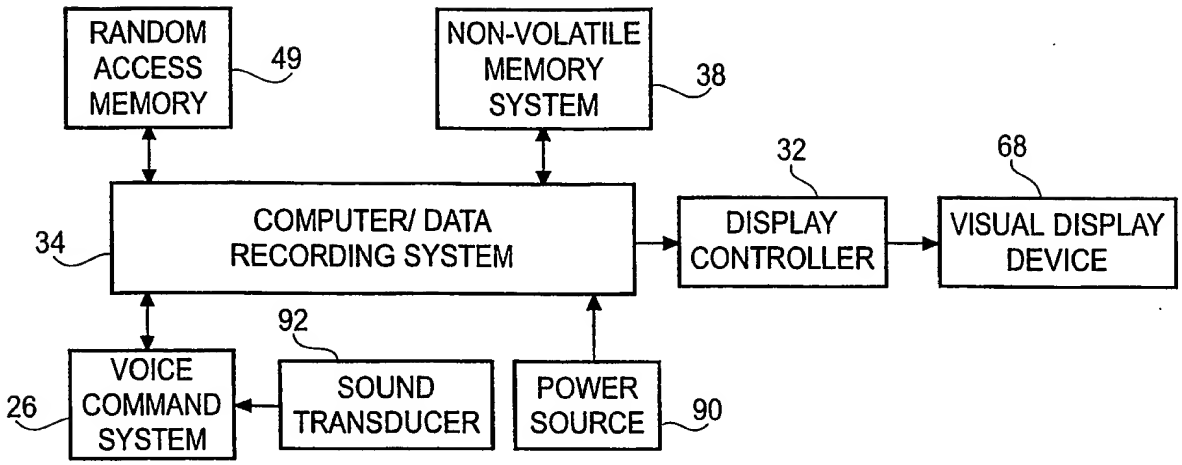
FIG. 11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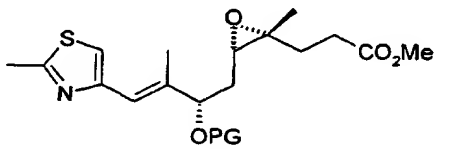
(54) Title: PROCESS FOR THE PRODUCTION OF EPOTHIOLONE B AND DERIVATIVES AS WELL AS INTERMEDIATE PRODUCTS FOR THIS PROCESS



(II)

(57) Abstract: The present invention is directed to a process for the production of epothilone compounds, the improvement comprising preparing said compounds by cyclization of a compound produced from an intermediate of formula (II) wherein PG is a protecting group.

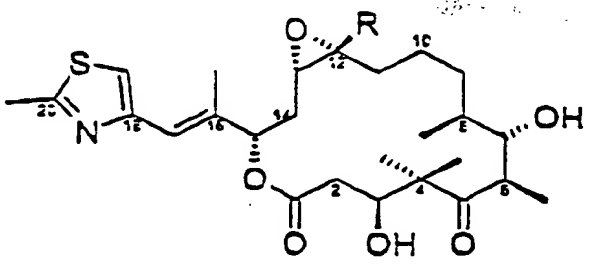
WO 01/07439 A2

Process for the Production of Epothiolone B and Derivatives as well as Intermediate Products for this Process

This application claims the benefit of the filing date of U.S. Provisional Application Serial No. 60/145,005, filed July 22, 1999.

This invention relates to a process for the production of epothilone B and derivatives as well as intermediate products for this process.

It is known that the natural substances epothilone A (R = H) and epothilone B (R = methyl) (compound I, DE 195 42 986 A1, DE 41 38 042 C2)



(I)

R = H, CH_3

have a fungicidal and cytotoxic effect. According to indications for in vitro activity against mammary and intestinal tumor cell lines, this family of compounds appears especially advantageous for the development of a pharmaceutical agent. Various working groups have successfully endeavored to synthesize these macrocyclic compounds. In this connection, the working groups start from various fragments of the macrocycle to synthesize the desired natural substances.

In any case, diastereomer-pure fragments as starting products and intermediate products are required for a successful epothilone synthesis. Diastereomer purity is often decisive for

the action and reliability of a pharmaceutical agent and thus a requirement for its production.

The total synthesis of epothilone A is described by Schinzer et al. in Chem. Eur. J. 1996, 2, No. 11, 1477-1482 and in Angew. Chem. 1997, 109, No. 5, pp. 543-544).

Epothilone derivatives were already described by Höfle et al. in WO 97/19086. These derivatives were produced starting from natural epothilone A or B.

Another synthesis of epothilone and epothilone derivatives was described by Nicolaou et al. in Angew. Chem. 1997, 109, No. 1/2, pp. 170-172. Nicolaou et al. also described the synthesis of epothilone A and B and several epothilone analogs in Nature, Vol. 387, 1997, pp. 268-272, and the synthesis of epothilone A and its derivatives in J. Am. Chem. Soc., Vol. 119, No. 34, 1997, pp. 7960-7973 as well as the synthesis of epothilone A and B and several epothilone analogs in J. Am. Chem. Soc., Vol. 119, No. 34, 1997, pp. 7974-7991.

Nicolaou et al. also describe in Angew. Chem. 1997, 109, No. 19, pp. 2181-2187 the production of epothilone A analogs using combinative solid-phase synthesis. Several epothilone B analogs are also described there.

A variable synthesis for the production of epothilone and different types of derivatives is known from WO 99/07692.

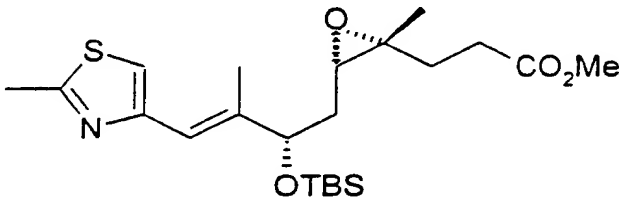
Other syntheses are described in PCT Applications WO 99/02514 and WO 99/01124.

Finally, the epothilone B-synthesis that is described by J. Mulzer et al. in Tetrahedron Letters 39 (1998) 8633-8636 can also be mentioned.

Because of the expected lability of the epoxide, in all previous syntheses of epothilone B, the corresponding (Z)-olefin was always epoxidated in the last step, whereby the diastereosection is 4:1 to 20:1 of the desired ß-isomer.

An object of this invention is to indicate a process for the production of epothilone B and epothilone B derivatives, in which the cis-epoxide is introduced at a considerably earlier time via dihydroxylation-monosulfonation of a suitable (E)-olefin, whereby the ß-configuration of the cis-epoxide is to come from the previous dihydroxylation. Other object are evident to one of ordinary skill.

These objects are achieved by a process using a compound of formula II



II

in which TBS stands for a tributylsilyl group. Instead of TBS, another suitable protective group can also be another suitable protective group can also be used as a starting compound, in which the epoxy group of the epothilone is already contained, and whereby this epoxy group remains unchanged in all subsequent reaction steps up to the end product.

Diagram 3 shows possible derivatizations that allow for the process according to the invention if compound 11 that is to be used and/or next steps 13 or 14 are modified as indicated. This invention therefore extends not only to the process for the production of epothilone B, but also to a process for the production of correspondingly modified derivatives that are derived from modified compounds 11, 13 or 14.

In addition, the invention also relates to the compounds of formulas 5 to 21, which are all new, as well as the correspondingly modified derivatives, which are obtained in the procedures indicated above and in diagram 3.

The selection of protective group (PG) in the 15-hydroxy group can be made with only routine experimentation. PG should outlast all subsequent reactions up to the macrolactonization, but in addition should also be removable in the presence of epoxide. The original TBS-function may not be removed without destroying the substrate; however, after converting the 15-OTBS derivative into the 15-OTES analog (TES = triethylsilyl), any additional synthesis step can be performed easily. Other suitable groups can be routinely determined TBS is preferably replaced by TES at steps 13, 14 or 15; at steps 15 and 17-19, PG is preferably TES.

The epoxide applied early thus was shown as stable under the following reaction conditions:

1. Reduction (neutral (DIBAH), ionic (selectride), metallic (Zn)
2. Oxidation (osmium tetroxide-sodium periodate)
3. Bases (fluoride in an aprotic solvent, DMAP, LDA, enolate). In this case, it is especially surprising

that C- and O-anions that were produced intramolecularly at a 1,5-interval to the epoxidic centers do not open the epoxide nucleophilically.

4. Electrophiles (acylation with acid chloride in the Yamaguchi reaction).

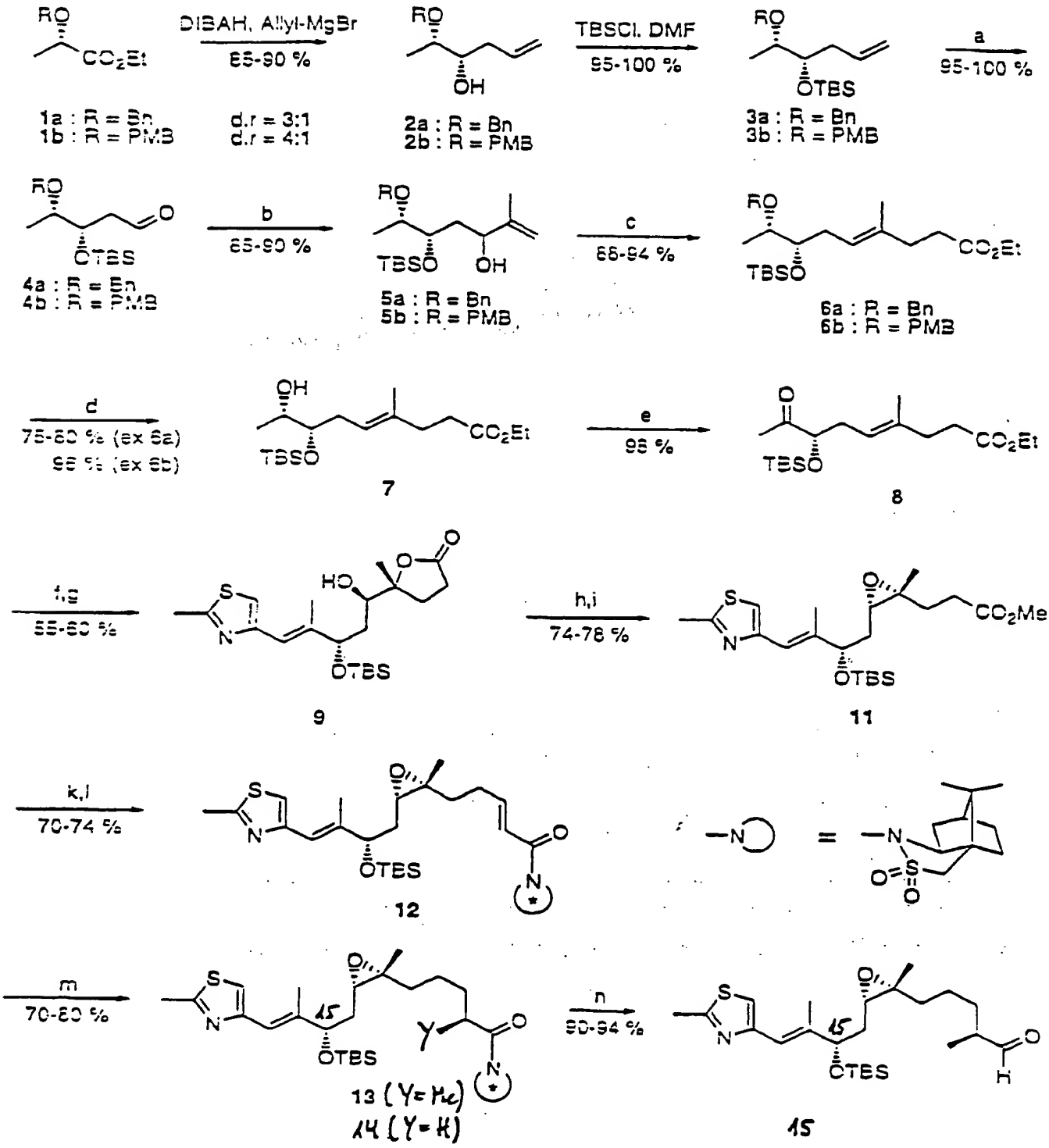
Of all the reagents used, only aqueous acid led to epoxide opening. Apart from the mechanistically valuable finding that does away with the preconception that epoxides are in any case highly reactive synthesis intermediate compounds, the early epoxide introduction also has considerable advantages for the production according to the invention of epothilone B and the corresponding derivatives:

The N-oxide formation on thiazole that is observed in the 12,13-epoxidation with peracid develops just like the separation of the 12,13-epimeric epoxide. No "false" epoxide is produced. The stereoselection of the aldol reaction is also considerably higher than for the 12,13-(Z)-olefin analogs of 21.

The examples that are tied to diagram 3 are used for a more detailed explanation of the invention.

Diagram 1

Synthesis of the Completely Functionalized C15-C7-Fragments of Epothilone B

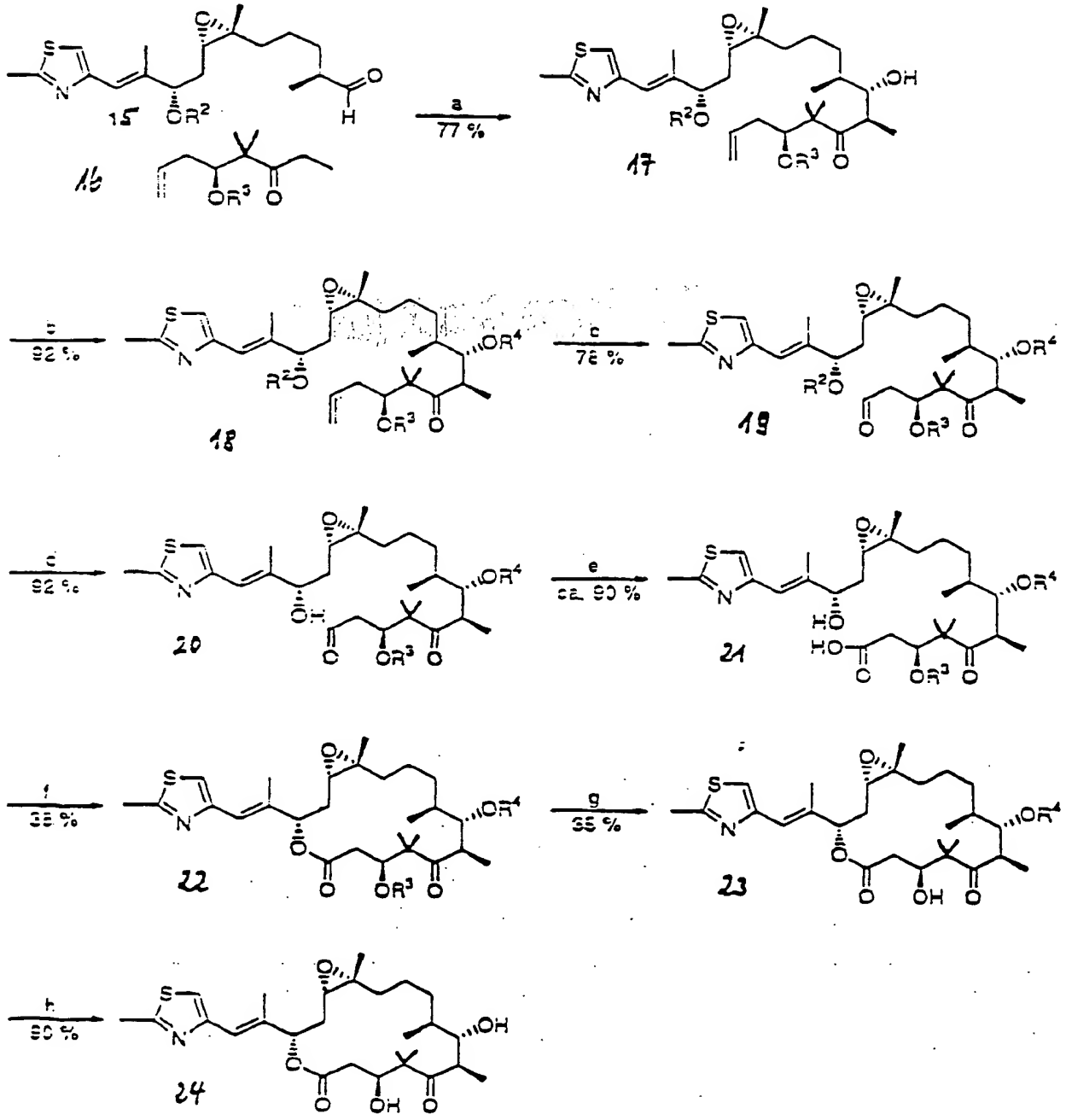


a) O_3, CH_2Cl_2, -78°C, PPh_3; b) isopropenyl-MgBr, THF, -10°C; c) $CH_3C(OEt)_3$, xylene, 120°C, 12 h; d) DDQ, CH_2Cl_2-H_2O, rt; e) Dess-Martin periodinane, CH_2Cl_2, rt, 12 h; f) AD-mix-ß, tBuOH-H_2O, rt, 20 h; g) Thz-CH_2-PBu_3Cl, KHMDS -78°C then 30°C; h) MsCl, NEt_3, CH_2Cl_2, 0°C, 30 min; i) K_2CO_3, MeOH, rt, 45 min; k) DIBAH, CH_2Cl_2, -90°C, 1 h; l) LiOH (in-situ), $(EtO)_2POCH_2CO(N°)$, then aldehyde, Et_2O-THF, rt, 30 min; m) L-selectrides, THF -78°C, 1 h, then HMPA, mel, -78°C to 0°C, 4 h; n) DIBAH, CH_2Cl_2, -80°C to -70°C, 2 h.

Bn = benzyl; PMB = p-methoxy-benzyl. All selectrides (cf. Aldrich Chemical Catalog) can be used in the process. L-selectride (lithium-tri-sec-butylborohydride) is preferred.

Diagram 2

Total Synthesis of Epothilone B (Epoxide Path)

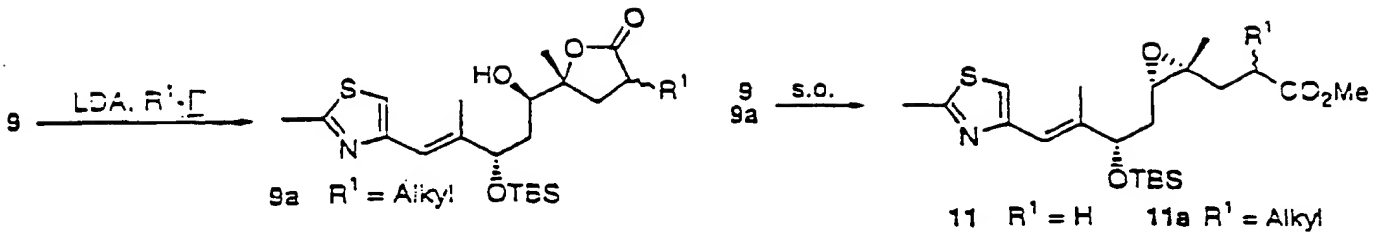


a) LDA, THF, -78°C; b) TrocCl, pyridine, CH_2Cl_2, rt; c) i. OsO_4, NMO; ii) $NaIO_4$; d) HF-Py, pyridine rt; e) $NaClO_2$, NaH_2PO_4, tBuOH, 2,3-dimethyl-2-butene; f) 2,4,6-trichlorobenzoyl chloride, NEt_3, then DMAP, toluene; g) HF-Py, pyridine rt; h) Zn, NH_4Cl, EtOH, reflux, 30 min.

Ketone 16 K.C. Nicolaou et al.: **J. Am. Chem. Soc. 1997, 119,** 7974-7991

Diagram 3

Derivatizations



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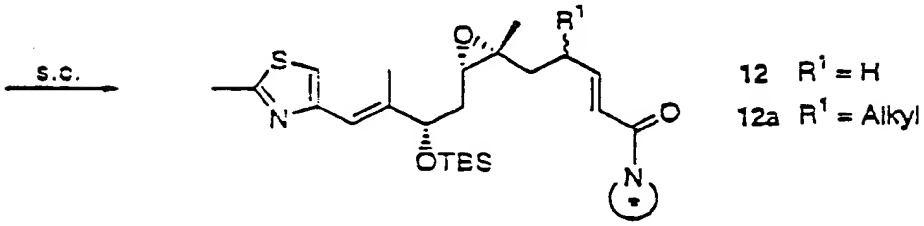
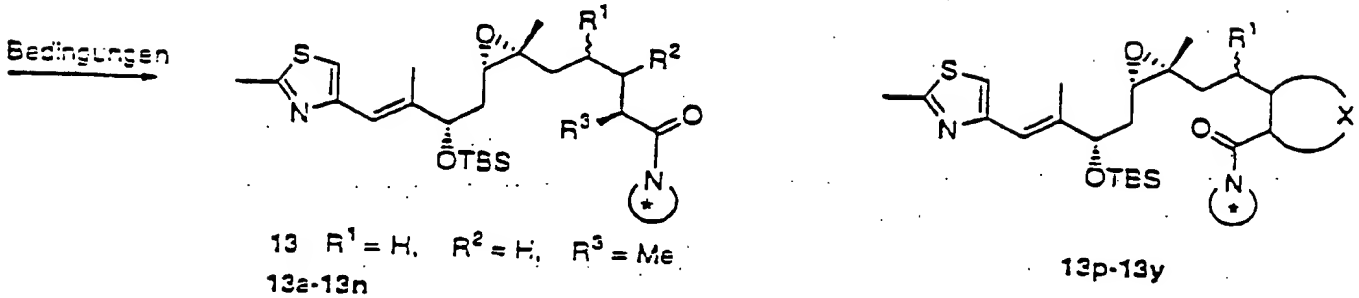
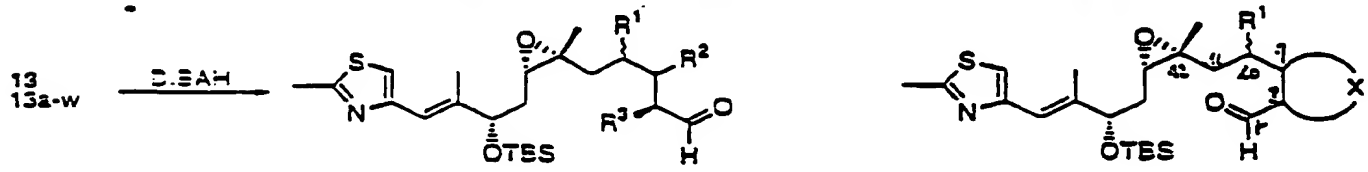


Conditions



Products	Conditions	Products	Conditions
13a R^1 = H, R^2 = H, R^3 = H,	L-Selectrides, NH_4Cl	13p R^1 = H, X = CH2	CH_2N_2, $Pd(OAc)_2$
13b R^1 = H, R^2 = Alkyl, R^3 = H	$(R^4)_2CuLi$, NH_4Cl	13q R^1 = Alkyl, X = CH2	
13c R^1 = H, R^2 = H, R^3 = Alkyl	L-Selectride , R^3-I	13r R^1 = H, X = O	TBHP, EuLi odor
13d R^1 = H, R^2 = Alkyl, R^3 = Alkyl	$(R^4)_2CuLi$, R^3-I	13s R^1 = Alkyl, X = O	mCPBA
13e R^1 = Alkyl, R^2 = H, R^3 = H	L-Selectrides, NH_4Cl	13t R^1 = H, X = N-Alkyl	MeONHR, NaOMe
13f R^1 = Alkyl, R^2 = Alkyl, R^3 =H	$(R^4)_2CuLi$, NH_4Cl	13u R^1 = Alkyl, X = N-Alkyl	odor-N-Aminophthalimide
13g R^1 = Alkyl, R^2 = H, R^3 = Alkyl	L-Selectrides, R^3-I		$Pb(OAc)_4$
13h R^1 = Alkyl, R^2 = Alkyl, R^3 = Alkyl	$(R^4)_2CuLi$, R^3-I	13v R^1 = H, X = RCHCH=CHCHR'	Diels-Alder- reaction
13i R^1 = H, R^2 = Aryl, R^3 = H	Aryl-MgBr, NH_4Cl	13w R^1 = Alkyl, X = RCHCH=CHCHR'	R—◇—R'
13k R^1 = H, R^2 = Aryl, R^3 = Alkyl	Aryl-MgBr, R^3-I	13x R^1 = H, 13y R^1 = Alkyl	
13m R^1 = Alkyl, R^2 = Aryl, R^3 = H	Aryl-MgBr, NH_4Cl	X =	
13n R^1 = Alkyl, R^2 = Aryl, R^3 = Alkyl	Aryl-MgBr, R^3-I		



Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

The entire disclosure of all applications, patents and publications, cited above, and U.S. Provisional Application Serial No. 60,145,005, filed July 22, 1999 is hereby incorporated by reference.

EXAMPLES

Experimental

$C_{18}H_{30}O_3Si$
Exact Mass: 322.1964
Mol. Wt.: 322.51
C, 67.03; H, 9.38

8.02 g (25 mmol) of alkene 3a is dissolved in 200 ml of absolute methylene chloride and mixed with 10 ml of absolute MeOH. After cooling to -78°C, a dried ozone/air mixture is introduced via a gas feed frit until the blue coloring begins. Air is allowed to blow through for two more minutes and then quenched by the addition of 19.67 g (75 mmol) of PPh_3 in portions, and it is allowed to thaw overnight. The solvent is removed as completely as possible in Rotavapor, and the remaining solid residue with use of preparative column chromatography (hexane/ethyl acetate/methylene chloride = 40:1:1) for separation of PPh_3, then Hx/EE 20:1 to 10:1. 7.90 g (98%) of aldehyde 4a is obtained as a colorless liquid.

^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (dd, J = 1.5, 2.0 Hz, 1H); 7.34-7.24 (m, 5H), 4.58 (d, J = 11.8 Hz, 1H), 4.45 (d, J = 11.8 Hz, 1H), 4.31 (dt, J = 6.3, 4.5 Hz, 1H), 3.58-3.51 (m, 1H), 2.69-2.62 (m, 1H), 2.51-2.43 (m, 1H), 1.14 (d, J = 6.3 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 201.8, 138.4, 128.4, 127.6, 71.0, 68.9, 46.0, 25.7, 17.9, 13.5, -4.7, -4.9.

IR (Film): ν_{max} 2956, 2857, 2712, 1730, 1472, 1255, 1102, 837, 778 cm^{-1}.

$C_{21}H_{36}O_3Si$
Exact Mass: 364.2434
Mol. Wt.: 364.5942
C, 69.18; H, 9.95; O, 13.16; Si, 7.70

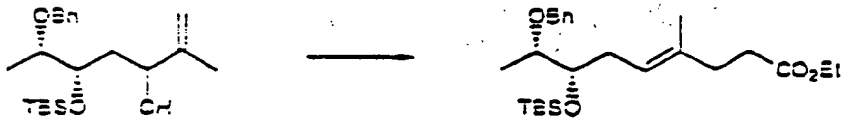
75 ml of isopropenylmagnesium bromide (0.5 M, THF) and 25 ml of absolute THF are cooled to -10°C under Ar atmosphere, and 9.14 g (28.3 mmol) of aldehyde 4a (dissolved in 20 ml of absolute THF) is slowly (about 20 minutes) added in drops at -10°C. It is allowed to thaw to 0°C within 45 minutes (TLC monitoring, Grignard optionally must also be added), the reaction mixture is poured into 150 ml of semi-saturated NH_4Cl solution and shaken out after 120 ml of ether is added. The aqueous phase is extracted twice more with ether (100 ml). The combined organic phases are dried ($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column chromatography (Hx/EE = 10:1) yields 9.48 g (92%) of allyl alcohol 5a (diastereomer mixture) as a colorless, viscous liquid.

Diastereomer 1

^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 4.98 (s, 1H), 4.80 (s, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.17 (d_{br}, J = 9.5 Hz, 1H), 4.02 (dt, J = 7.4, 4.5 Hz, 1H), 3.61-3.54 (m, 1H), 2.71 (d_{br}, J = 3.5 Hz, 1H), 1.84-1.75 (m, 1H), 1.72 (s, 3H), 1.65-1.57 (m, 1H), 1.14 (d, J = 6.5 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), -0.02 (s, 3H).

Diastereomer 2

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 4.99 (s, 1H), 4.83 (s, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.20 (dd, J = 8.0, 3.5 Hz, 1H), 3.90 (dt, J = 8.5, 4.3 Hz, 1H), 3.47 (dq, J = 6.4, 4.3 Hz, 1H), 2.97 (s_{br}, 1H), 1.86 (dt, J = 14.2, 4.1 Hz, 1H), 1.67 (s, 3H), 1.57 (dt, J = 14.6, 8.5 Hz, 1H), 1.10 (d, J = 6.4 Hz, 3H), 0.80 (s, 9H)



5a 6a

$C_{25}H_{42}O_4Si$
Exact Mass: 434.2852
Mol. Wt: 434.6541
C, 69.08; H, 9.74; O, 14.72; Si, 6.46

8.02 g (22 mmol) of allyl alcohol 5a (diastereomer mixture) is dissolved in 120 ml of absolute xylene and mixed with 32 ml (176 mmol) of triethylorthoacetate and 4 drops of propionic acid. With a light Ar stream through a thin capillary, it is stirred for 16-20 hours at 120°C, whereby the ethanol that is produced is distilled off via a small distillation apparatus. After the reaction is completed (TLC monitoring), the solvent is distilled off in Rotavapor (30 mbar, 50°C, then complete vacuum), and the crude product is purified by column chromatography (Hx/EE = 40:1 gradient 20:1). 8.77 g (92%) of 6a is obtained as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (m, 5H); 5.20 (t, J = 6.4 Hz, 1H); 4.57 (d, J = 12 Hz, 1H), 4.48 (d, J = 12 Hz, 1H),

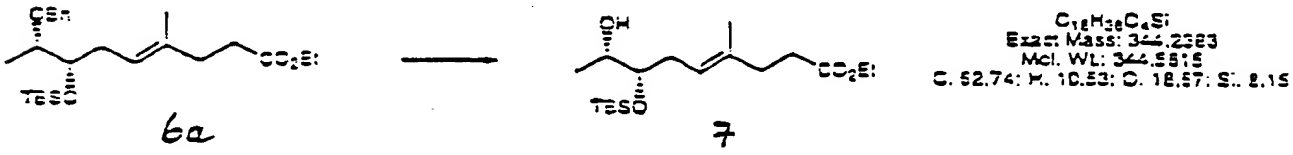
4.11 (q, J = 7.2, 2H), 3.68 (m, J = 4 Hz, 1H), 3.46 (dt, J = 6.3, 4.5 Hz, 1H), 2.40-2.34 (m, 1H), 2.32-2.24 (m, 2H), 2.14-2.04 (m, 1H), 1.60 (s, 3H), 1.23 (t, J = 7.2 Hz, 2H), 1.11 (d, J = 6.4 Hz, 3H), 0.84 (s, 9H), -0.02 (s, 3H), -0.05 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 173.5, 139.1, 134.5, 128.2, 127.5, 127.4, 124.0, 122.4, 77.3, 74.0, 71.0, 60.2, 34.8, 33.1, 30.1, 25.8, 18.0, 16.1, 14.2, 14.0, -4.60, -4.61.

IR (Film): ν_{max} 2956, 2930, 2887, 2857, 1737, 1472, 1462, 1454, 1370, 1300, 1255, 1155, 1098, 939, 836, 776, 737 cm^{-1}.

HRMS (EI) Cld. for $C_{25}H_{42}O_4Si$ 434.2852, Fnd. 434.2845

$[\alpha]^{20}_D$ = -3.9 (c = 1.2. $CHCl_3$)



912 mg (2.10 mmol) of 6a is dissolved in 40 ml of methylene chloride and 2 ml of water, mixed with 2.86 g (12.6 mmol) of DDQ and stirred vigorously for exactly 3 hours at room temperature. The reaction mixture is diluted with 100 ml of ether and washed with $NaHCO_3$ (aqueous, saturated) (2x 40 ml). The combined aqueous phases are diluted with 80 ml of water and extracted with ether (2x 50 ml). The combined organic phases are washed with brine (50 ml), dried ($MgSO_4$), and the solvent is removed in

Rotavapor. Preparative column chromatography (Hx/EE = 10:1) yields 575 mg (80%) of alcohol 7 as a colorless liquid.

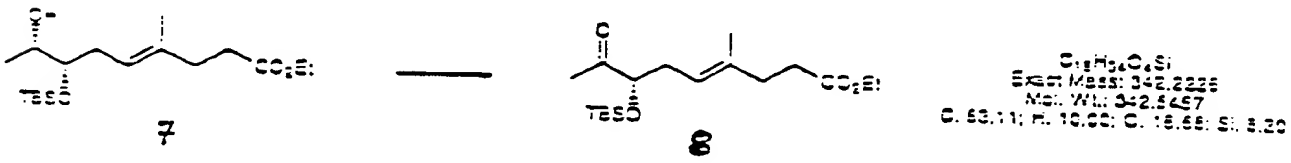
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (dt, J = 7.3, 1.0 Hz, 1H), 4.09 (q, J = 7.07 Hz, 2H), 3.56 (m, 1H), 3.42 (dt, J = 7.2, 4.4 Hz, 1H), 2.40-2.26 (m, 5H), 2.15-2.07 (m, 2H), 1.61 (m, 3H), 1.23 (t, J = 7.0 Hz, 3H), 1.09 (d, J = 6.5 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 173.7, 136.1, 120.9, 77.0, 69.0, 60.7, 35.2, 33.5, 33.0, 26.2, 20.3, 18.5, 16.6, 14.6, -3.8, -4.3.

IR (Film): ν_{max} 3513 (br), 2932, 2874, 2855, 1738, 1463, 1372, 1255, 1157, 1088, 836, 777 cm^{-1}.

HRMS (EI) Cld. for ($M^+ - C_4H_9$) 287.168, Fnd. 287.168 ± 5 ppm

$[\alpha]^{20}_D$ = +20.2 (c = 1.08, $CHCl_3$)



7 8

($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column chromatography (Hx/EE = 10:1) yields 945 mg (92%) of ketone 8 as a colorless liquid.

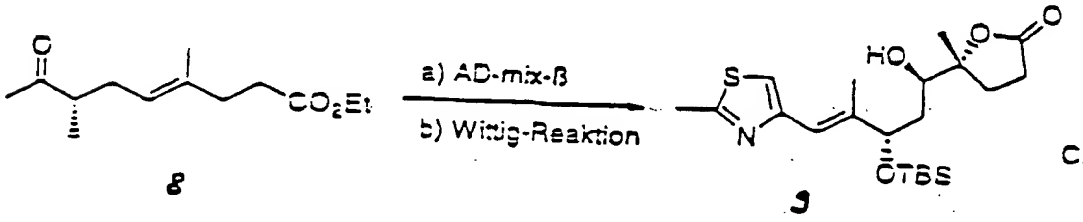
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (t, 1H, J = 6.8 Hz, 1H); 4.10 (q, J = 7.0 Hz, 2H), 3.97 (dd, J = 6.5, 5.5 Hz, 1H), 2.40-2.20 (m, 6H), 2.12 (s, 3H), 1.59 (s, 3H), 1.23 (t, J = 7.0 Hz, 1H), 0.89 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 212.5, 173.7, 137.0, 119.7, 79.2, 60.7, 35.1, 33.9, 33.7, 33.4, 26.1, 25.9, 18.5, 16.6, 14.6, -4.5, -4.6.

IR (Film): ν_{max} 2932, 2875, 2858, 1737, 1351, 1256, 1203, 1160, 1137, 1102, 959, 927, 899, 839, 779 cm^{-1}.

HRMS (EI) Cld. for (M^+-CH_3) 327.1992. Fnd. 327.199 ± 0.0016

$[\alpha]^{20}_D$ = -19.4 (c = 1.05, $CHCl_3$)



8 9

$C_{21}H_{35}NO_4SSi$
Exact Mass: 425,21
Mol. Wt.: 425,66
C, 59,25; H, 8,29; N, 3,29

a) 830 mg (2.42 mmol) of 8 is dissolved in 30 ml of $_t$BuOH-H_2O (1:1) and mixed with 1.5 g of $NaHCO_3$, 5.0 g of AD-Mix-ß and 230 mg of methanesulfonamide. After 36-48 hours at room temperature while being stirred vigorously, it is quenched by

adding 5 g of sodium sulfite (10 more minutes of stirring). After 25 ml of H_2O and 100 ml of methylene chloride are added, the phases are separated, and the aqueous phase is extracted with methylene chloride (3 x 30 ml). The combined organic phases are dried ($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column chromatography (Hx/EE = 2:1, $R_{f\ (3:1)}$ = 0.09 to 0.29) yields 942 mg of product mixture 8a.

IR (Film): ν_{max} 3432, 2933, 2858, 1736, 1377, 1256, 1229, 1095, 837, 778 cm^{-1}.

b) 1.82 g of Wittig salt (5.2 mmol) is dissolved in 30 ml of absolute THF under Ar atmosphere, cooled to -78°C, and 10.4 ml of KHMDS (0.5 M, toluene) is added in drops and stirred for 45 minutes at -78°C. Then, 920 mg of 8a (dissolved in 2.5 ml of THF) is added smoothly in drops. It is allowed to stir for 5 more minutes at -78°C, the cooling bath is then quickly exchanged for an approximately 40°C water bath and allowed to thaw. After 5 minutes, the bath is removed, and it is allowed to stir for another 5 minutes before being quenched with 50 ml of NH_4Cl (saturated, aqueous) and 75 ml of ether. The aqueous phase is extracted with ether (2x 30 ml). The combined organic phases are dried ($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column chromatography (Hx/EE = 2:1) yields 632 mg (61% on both synthesis steps) of alkene 9 as a colorless, viscous liquid.

^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.47 (s, 1H), 4.41 (dd, J = 8.5, 4.5 Hz, 1H), 3.67 (d, J = 10.0 Hz, 1H), 3.45 (s,

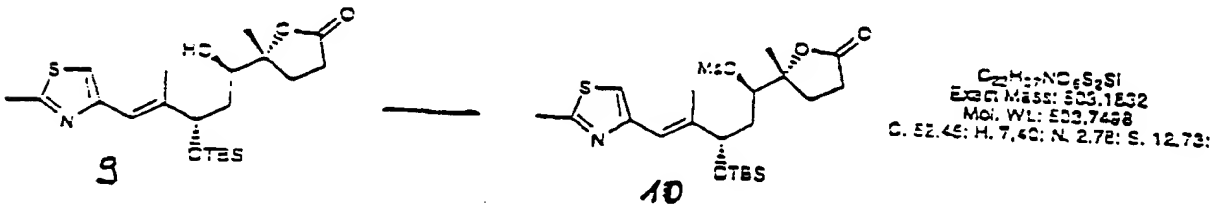
1H), 2.71-2.61 (m, 1H), 2.68 (s, 3H), 2.66-2.46 (m, 1H), 2.37-2.28 (m, 1H), 1.99 (s, 3H), 1.80-1.66 (m, 2H), 1.70 (dd, J = 14.3, 4.8 Hz, 1H), 1.34 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 177.6, 165.1, 152.9, 141.4, 120.4, 116.3, 88.0, 79.9, 76.7, 37.1, 30.9, 29.9, 26.2, 23.6, 19.6, 18.4, 14.1, -4.0, -4.8.

IR (Film): ν_{max} 3469, 2955, 2943, 2930, 2910, 2892, 2856, 1768, 1656, 1505, 1462, 1386, 1252, 1066, 838 cm^{-1}.

HRMS (EI) Cld. for C21H35NO4SiS 425.2056 Fnd. 425,2060 ± 0.0025

$[\alpha]^{20}_D$ = -27.1 (c = 1.0, $CHCl_3$)



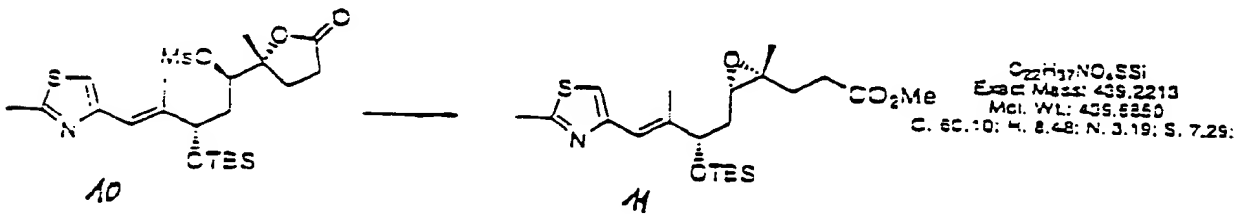
$C_{22}H_{37}NO_6S_2Si$
Exact Mass: 503.1832
Mol. Wt.: 503.7498
C, 52.45; H, 7.40; N, 2.78; S, 12.73;

313 mg (0.737 mmol) of alcohol 9 is dissolved under Ar atmosphere in 5 ml of absolute methylene chloride and mixed at 0°C with 0.31 ml of absolute triethylamine and 0.09 ml of methanesulfonic acid chloride. After 30 minutes, it is quenched with 10 ml of $NaHCO_3$ (aqueous, saturated), the phases are separated, and the aqueous phase is extracted with methylene chloride (3x 10 ml). The combined organic phases are dried

($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column chromatography (Hx/EE = 4:1) yields 283 mg (76%) of mesylate 10 as a strongly viscous, yellowish liquid.

^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.56 (s, 1H), 4.57 (dd, J = 8.0, 2.5 Hz, 1H), 4.41 (dd, J = 8.8, 4.8 Hz, 1H), 3.13 (s, 3H), 2.68 (s, 3H), 2.60-2.53 (m, 2H), 2.02 (d, J = 1.0 Hz, 3H), 2.07-1.81 (m, 4H), 1.42 (s, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 175.5, 165.0, 153.2, 138.7, 122.1, 117.2, 86.5, 83.8, 75.7, 39.6, 38.0, 31.2, 28.8, 26.2, 21.7, 19.7, 18.5, 13.1, -4.3, -4.6.



256 mg (0.508 mmol) of mesylate 10 is dissolved in 10 ml of absolute methanol and mixed with finely pulverized potassium carbonate. After 45 minutes at room temperature, it is diluted with 30 ml of ether and then filtered. Saturated NH_4Cl solution (15 ml) is added to the filtrate until two clear phases form. The phases are separated, and the aqueous phase is extracted with ether (3x 10 ml). The combined organic phases are dried ($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column

chromatography (Hx/EE = 5:1) yields 202 mg (90%) of epoxide 11 as a colorless, viscous liquid.

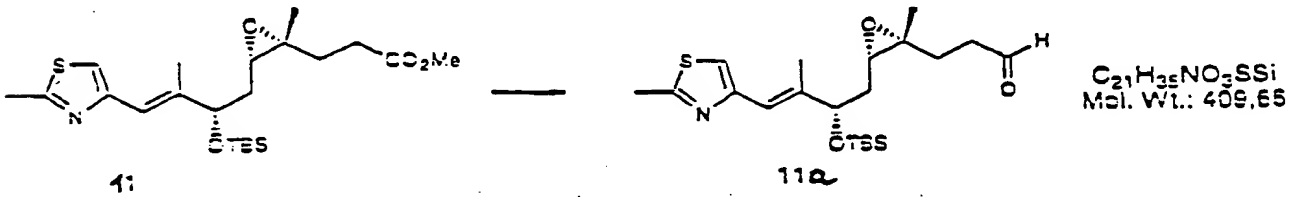
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.49 (s, 1H), 4.32 (dd, J = 9.0, 3.5 Hz, 1H), 3.65 (s, 3H), 2.89 (dd, J = 7.0, 4.5 Hz, 1H), 2.68 (s, 3H), 2.46-2.40 (m, 2H), 1.99 (d, J = 1.5 Hz, 1H), 1.94-1.77 (m, 3H), 1.63-1.55 (m, 1H), 1.26 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 173.6, 164.9, 153.4, 142.4, 119.3, 115.8, 76.7, 62.8, 60.4, 52.1, 36.3, 30.5, 28.6, 26.3, 22.5, 19.6, 18.6, 14.4, -4.2, -4.7.

IR (Film): ν_{max} 2955, 2874, 2857, 1740, 1656, 1505, 1439, 1380, 1312, 1230, 1180, 1077, 835, 778 cm^{-1}.

HRMS (EI) Cld. for $C_{22}H_{37}NO_4SiS$ 439.2213 Fnd. 439.221 ± 0.0025.

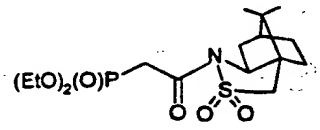
$[\alpha]^{20}_D$ = -12.6 (c = 1.04, $CHCl_3$)

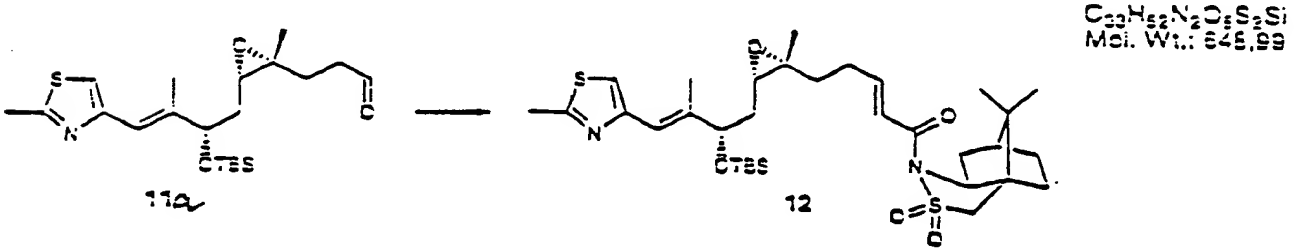


176 mg (0.40 mmol) of epoxide 11 is dissolved in 6 ml of absolute MC under argon and slowly (about 5 minutes) mixed with 0.29 ml (0.44 mmol) of DIBAH (1.5M toluene) at -95°C. It is allowed to come to -85°C within 45 minutes, mixed with 0.15 ml of

NH_4Cl solution and 10 ml of ether while being stirred vigorously, and it is allowed to thaw quickly. After sufficient $MgSO_4$ is added, it is allowed to stir for 1-2 hours and filtered off. After the solvent is removed in Rotavapor, the crude aldehyde is purified by column chromatography (Hx/EE = 3:1), and 140 mg (85%) of aldehyde 11a is obtained as a colorless oil.

IR (Film): ν_{max} 2930, 2781, 1727, 1677, 1076, 919, 836.





$C_{33}H_{52}N_2O_5S_2Si$
Mol. Wt.: 648.99

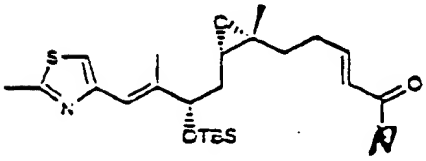
11a 12

4 ml of absolute ether at 0°C and 0.32 ml of nBuLi (1.6M, hexane, 0.51 mmol) are introduced under Ar atmosphere and mixed with 0.36 ml of THF/H_2O (19:1, 1 mmol of H_2O). After 5 minutes, 193 mg of phosphonate (0.49 mmol, dissolved in 1 ml of THF) is added in drops, and after another 10 minutes, 135 mg (0.33 mmol, dissolved in 1 ml of THF) of aldehyde 11a is added in drops. The cooling bath is removed, and after 30 minutes at room temperature, it is quenched with 4 ml of saturated NH_4Cl solution, the phases are separated, and the aqueous phase is extracted with ether (2x 5 ml). The combined organic phases are dried ($MgSO_4$), and the solvent is removed in Rotavapor.

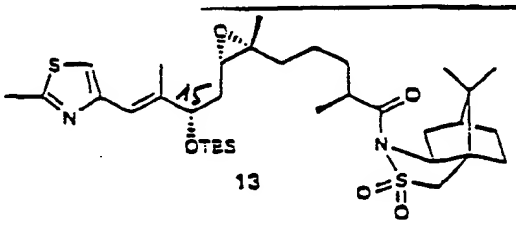
Preparative column chromatography (Hx/EE = 3:1) yields 194 mg (91%) of enoylsultam 12 as a viscous oil, which solidifies like a foam after freezing-out.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (dt, J = 14.8, 7.3 Hz, 1H), 6.91 (s, 1H), 6.55 (d, J = 14.8 Hz, 1H), 6.49 (s, 1H), 4.32 (dd, J = 8.8, 3.8 Hz, 1H), 3.90 (dd, J = 7.3, 5.3 Hz, 1H), 3.48 (d, J = 13.8 Hz, 1H); 3.40 (d, J = 13, 8 Hz, 1H), 2.89 (dd, J = 7.5, 4.5 Hz, 1H), 2.68 (s, 3H), 2.42-2.33 (m, 2H), 2.13-2.02 (m, 2H), 1.99 (s, 3H), 1.95-1.81 (m, 5H), 1.71-1.51 (m, 4H), 1.27 (s, 3H), 1.14 (s, 3H), 0.95 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 164.8, 164.3, 153.4, 149.9, 142.4, 121.6, 119.3, 115.8, 76.8, 65.5, 62.6, 60.7, 53.5, 50.7, 48.8, 48.2, 45.1, 38.9, 36.2, 33.3, 31.9, 28.8, 26.9, 26.2, 22.6, 21.2, 20.3, 19.6, 18.6, 14.4, -4.2, -4.7.

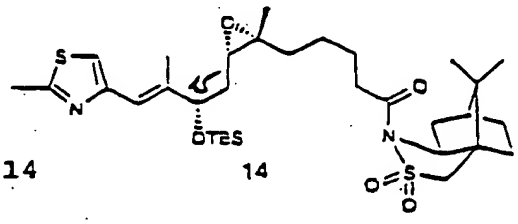


12



13

$C_{33}H_{55}N_2O_5S_2Si$
Mol. Wt.: 655,04



14

$C_{33}H_{54}N_2O_5S_2Si$
Mol. Wt.: 651,01

Conversion at Stage 13 or 14 of OTBS to OTES

172 mg (0.265 mmol) of sultam 12 is dissolved in 5 ml of absolute THF and mixed at -95°C with 0.32 ml of L-selectrides (1.0 M, THF, 0.32 mmol) and heated within 45 minutes to -40°C. After another 15 minutes, it is cooled to -78°C, and after 0.12 ml of HMPA is added, it is mixed with 0.132 ml of MeI. Then, it is heated within 3 hours to 0°C, and after another 2 hours at 0°C, it is quenched by adding 5 ml of NH_4Cl and 10 ml of ether. The phases are separated, and the aqueous phase is extracted with ether (2x 5 ml). The combined organic phases are dried ($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column chromatography (Hx/EE = 3:1) yields 90 mg of **13** and 85 mg of **14**.

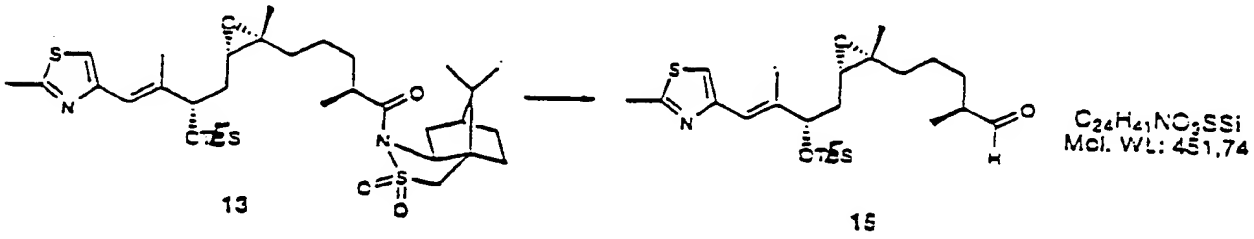
Compound 13

^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.47 (s, 1H), 4.29 (dd, J = 9.0, 3.5 Hz, 1H), 3.85 (t, J = 6.3 Hz, 1H), 3.44 (d, J = 13.5 Hz, 1H), 3.37 (d, J = 3.5 Hz, 1H), 3.07-3.97 (m, 1H), 2.83 (dd, J = 8.0, 4.0 Hz, 1H), 2.66 (s, 3H), 2.02-1.98 (m, 2H), 1.98 (d, J = 1.0 Hz, 3H), 1.92-1.68 (m, 5H), 1.57-1.26 (m, 8H), 1.22 (s, 3H), 1.16 (d, J = 7.0 Hz, 3H), 1.11 (s, 3H), 0.92 (s, 3H), 0.86 (s, 9H), 0.05 (s, 3H), -0.01 (s, 3H).

Compound 14

^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.49 (s, 1H), 4.31 (dd, J = 9.0, 3.5 Hz, 1H), 3.83, (dd, J = 7.3, 5.3 Hz, 1H), 3.45 (d, J = 13.6 Hz, 1H), 3.39 (d, J = 13.6 Hz, 1H), 2.86 (dd, J = 7.8, 4.3 Hz, 1H), 2.75-2.63 (m, 2H), 2.68 (s, 3H), 2.12-2.03 (m, 2H), 2.00 (d, J = 1.0 Hz, 3H), 1.93-1.80 (m, 4H), 1.72-1.30 (m,

9H), 1.24 (s, 3H), 1.12 (s, 3H), 0.93 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H).

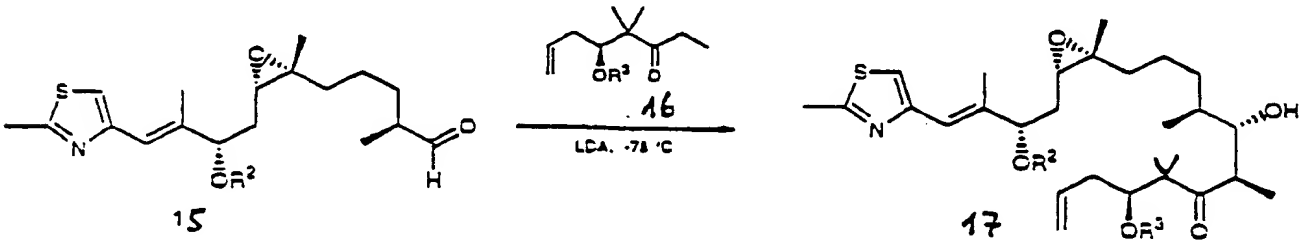


50 mg (0.075 mmol) of sultam 13 is dissolved under argon in 2.5 ml of absolute methylene chloride and mixed slowly with 0.083 ml (0.083 mmol) of DIBAH (1.0 M, toluene) at -95°C. It is allowed to come to -75°C within 2-2.5 hours while being stirred vigorously with 0.05 ml of MeOH and 0.1 ml of NH_4Cl solution, as well as 5 ml of ether, and it is allowed to thaw quickly. After sufficient $MgSO_4$ is added, it is allowed to stir for about 1 hour (even overnight) and filtered off. After the solvent is removed in Rotavapor, the crude aldehyde is purified by column chromatography (Hx/EE = 3:1), and 24 mg (71%) of aldehyde 15 is obtained as a waxy solid.

^1H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, J = 5.0 Hz, 1H), 6.90 (s, 1H), 6.49 (s, 1H), 4.31 (dd, J = 9.0, 4.0 Hz, 1H), 2.87 (dd, J = 7.0, 4.5 Hz, 1H), 2.68 (s, 3H), 2.36-2.26 (m, 1H), 2.00 (s, 3H), 1.92-1.84 (m, 1H), 1.74-1.64 (m, 1H), 1.60-1.52 (m, 1H), 1.50-1.32 (m, 5H), 1.26 (s, 3H), 1.08 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 205.2, 164.9, 153.4, 142.5, 119.2, 115.8, 76.7, 62.4, 61.1, 46.7, 36.4, 33.6, 31.0, 26.2, 23.3, 22.7, 19.6, 18.6, 14.4, 13.7, -4.2, -4.7.

Aldol Reaction



Example: R^2 = TES, R^3 = TBS

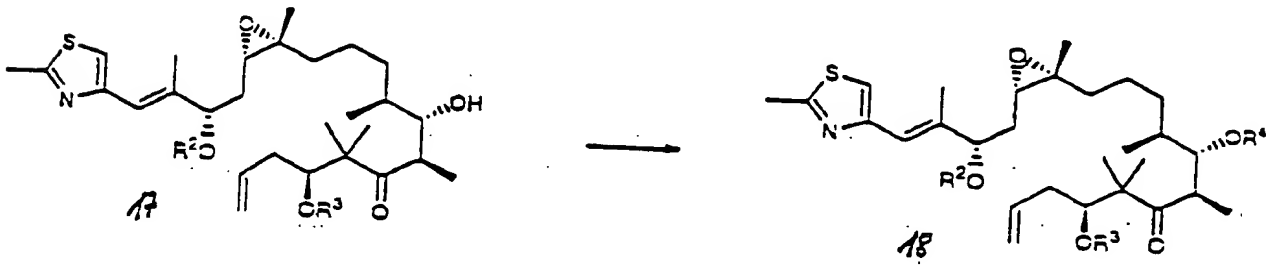
1.75 ml (1.23 mmol) of isopropylamine is dissolved in 4 ml of absolute THF and mixed at -45°C with 0.75 ml of nBuLi (1.6 M in hexane; 1.20 mmol), heated to 0°C after 5 minutes and stirred for 20 minutes at 0°C. After cooling to -78°C, 345 mg (1.21 mmol) of ketone 16 (dissolved in 1 ml of THF) is added in drops within 2 minutes, and the reaction mixture is heated to -40°C within 30 minutes. It is again cooled to -78°C, and 532 mg (1.18 mmol) of aldehyde 15 (dissolved in 1.5 ml of THF) is added in drops within 2-3 minutes. After 15 minutes at -78°C, it is quenched with 4 ml of saturated NH_4Cl solution while being stirred vigorously (initially slowly then quickly added), 6 ml of ether is added, and the cooling bath is replaced by a water bath. After thawing, some water is added, and the phases are separated after shaking out. Extraction with ether, drying ($MgSO_4$),

removal of the solvent and subsequent column chromatography (hexane/ethyl acetate 10:1 → 5:1) yield 668 mg (77%) of desired main isomer 17 as a colorless, viscous liquid.

Compound 17 (R^2 = TES, R^3 = TBS)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.93 (s, 1H), 6.51 (s, 1H), 5.72 (ddt, J = 17.1, 10.0, 7.0 Hz, 1H), 4.99 (m, 2H), 4.33 (dd, J = 9.0, 3.5 Hz, 1H), 3.92 (d, J = 6.3, 4.3 Hz, 1H), 3.49 (s, 1H), 3.31 (d, J = 9.0 Hz, 1H), 3.25 (q, J = 7.0 Hz, 1H), 2.88 (dd, J = 7.5, 4.0 Hz, 1H), 2.70 (s, 3H), 2.24-2.06 (m, 2H), 2.01 (d, J = 1.0 Hz, 3H), 1.95-1.87 (m, 1H), 1.82-1.72 (m, 1H), 1.63-1.45 (m, 5H), 1.41-1.30 (m, 1H), 1.28 (s, 3H), 1.18 (s, 3H), 1.20-1.05 (m, 1H), 1.12 (s, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.83 (d, J = 7.0 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 222.5, 164.4, 153.1, 142.2, 136.3, 118.8, 116.7, 115.3, 76.5, 76.4, 74.9, 62.1, 61.1, 54.3, 41.1, 39.6, 36.0, 35.6, 33.4, 33.1, 26.05, 25.9, 23.4, 22.7, 22.4, 19.4, 19.2, 18.24, 18.21, 15.3, 14.0, 9.7, -3.5, -4.90, -4.6, -5.1.

7-OH Protection



Example: R^2 = TES, R^3 = TBS, R^4 = Troc

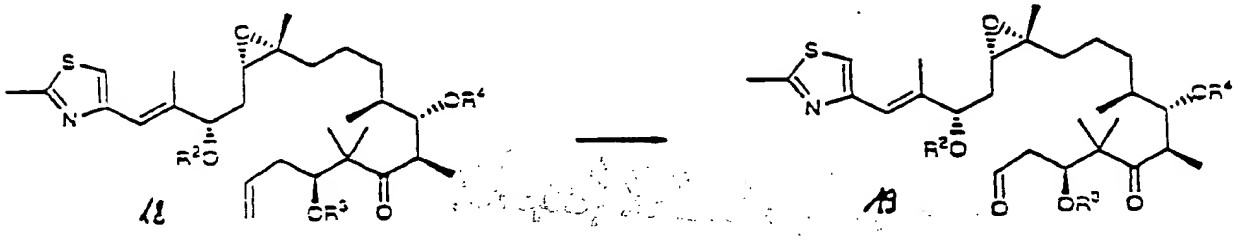
200 mg (0.27 mmol) of aldol 17 is dissolved in 10 ml of methylene chloride and 5 ml of pyridine and mixed at 20°C (water bath) with 0.5 ml (2.4 mmol) of chloroformic acid-2,2,2-trichloroethyl ester and stirred for 30-45 minutes at room temperature. For working-up, the reaction mixture is shaken out with 50 ml of saturated $NaHCO_3$ solution and 40 ml of methylene chloride. Extraction with methylene chloride, drying ($MgSO_4$), removal of the solvent and subsequent column chromatography (hexane/ethyl acetate 10:1) yield 231 mg (94%) of desired product 18 as a colorless oil.

Compound 18 (R^2 = TES, R^3 = TBS, R^4 = Troc)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.92 (s, 1H), 6.51 (s, 1H), 5.79 (ddt, J = 16.6, 10.5, 7.0 Hz, 1H), 5.05-4.97 (m, 2H), 4.85 (d, J = 12.1 Hz, 1H), 4.81 (dd, J = 7.0, 4.5 Hz, 1H), 4.69 (d, J = 12.1 Hz, 1H), 4.33 (dd, J = 9.0, 3.5 Hz, 1H), 3.75 (dd, J = 6.5, 4.0 Hz, 1H), 3.44 (m, 1H), 2.88 (dd, J = 7.5, 4.0 Hz, 1H), 2.70 (s, 3H), 2.28-2.19 (m, 1H), 2.06-1.95 (m, 1H), 2.02 (s, 3H), 1.92-1.84 (m, 1H), 1.75-1.65 (m, 1H), 1.57-1.41 (m, 5H), 1.33-1.11 (m, 2H), 1.30 (s, 3H), 1.27 (s, 3H), 1.21-1.12 (m, 1H), 1.07 (d, J = 7.0 Hz, 3H), 1.04 (s, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 215.6, 164.4, 154.2, 153.1, 142.1, 136.4, 118.9, 116.6, 115.4, 94.8, 82.9, 78.1, 76.6, 76.4, 62.1, 60.8, 54.0, 42.3, 39.4, 36.0, 35.0, 33.3, 31.8, 26.1, 25.9, 24.0, 22.7, 22.3, 20.0, 19.2, 18.23, 18.21,

16.1, 14.0, 11.5, -3.6, -3.9, -4.6, -5.1. **IR** (film) $\tilde{\upsilon}_{max}$ = 2956, 2930, 2858, 1760, 1699, 1472, 1384, 1251, 1081, 992, 928, 836, 777, 732. **Rotation:** $[\alpha]^{20}_{D}$ = -30 (c = 1.4, CH_2Cl_2). **Analysis** Cld. for $C_{43}H_{74}Cl_3NO_7SSi_2$ (911,65): C 56.65, H 8.18, N 1.54, Fnd.: C 56.54 H 8.18 N 1.47.

Dihydroxylation/Glycol Cleavage



Example: R^2 = TES, R^3 = TBS, R^4 = Troc

148 mg (0.162 mmol) of alkene 18 is dissolved in 8 ml of THF-tBuOH (1:1) and mixed with 2 mg of OsO4 (5 mol%) and 0.89 ml of NMO (0.2 M in H_2O, 0.178 mmol). After 16 hours of stirring at 25°C, it is shaken out vigorously and for a long time with 10 ml of $Na_2S_2O_3$ (10% in H_2O) and 15 ml of methylene chloride. The phases are separated, and the aqueous phase is extracted three more times with methylene chloride. Drying ($MgSO_4$), removal of the solvent and filtration via a short silica gel column (hexane/ethyl acetate 1:1) yields 131 mg (86%) of diol as an isomer mixture, which is further used without additional purification.

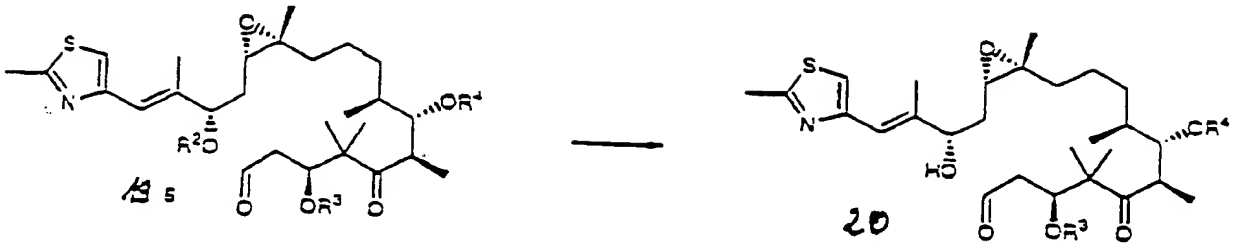
131 mg (0.139 mmol) of diol is dissolved in 15 ml of ethanol and 3 ml of H_2O and mixed with 90 mg (0.420 mmol) of $NaIO_4$.

After three hours of stirring at 25°C, it is shaken out with 30 ml of semi-saturated $NaHCO_3$ solution and 30 ml of ether, and the phases are separated. Extraction with ether, drying ($MgSO_4$), removal of the solvent and subsequent column chromatography (Hexane/ethyl acetate 10:1 → 5:1) yield 115 mg (78% in terms of alkene) of aldehyde 19 as a colorless oil.

Compound 19 (R^2 = TES, $R^{3'}$ = TBS, R^4 = Troc)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (dd, J = 2.0, 1.0 Hz, 1H), 6.92 (s, 1H), 6.50 (s, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.74 (dd, J = 7.5, 4.0 Hz, 1H), 4.67 (d, J = 11.8 Hz, 1H), 4.36-4.29 (m, 2H), 3.49-3.38 (m, 1H), 2.88 (dd, J = 7.5, 4.0 Hz, 1H), 2.70 (s, 3H), 2.67 (ddd, J = 17.5, 4.5, 1.0 Hz, 1H), 2.39 (ddd, J = 17.5, 5.5, 2.0 Hz, 1H), 2.39 (s, 3H), 1.88 (ddd, J = 13.9, 9.4, 4.0 Hz, 1H), 1.76-1.66 (m, 1H), 1.60-1.40 (m, 5H), 1.35-1.10, (m, 2H), 1.33 (s, 3H), 1.26 (s, 3H), 1.20 (d, J = 6.5 Hz, 1H), 1.02 (s, 3H), 0.97 (d, J = 6.5 Hz, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 215.4, 200.2, 164.2, 154.2, 153.0, 142.1, 118.9, 115.4, 94.7, 82.3, 76.65, 76.3, 72.3, 62.1, 60.8, 53.4, 49.3, 42.2, 35.9, 34.9, 3.33, 31.9, 25.87, 25.85, 23.0, 22.6, 22.3, 20.0, 19.2, 18.2, 18.1, 15.9, 14.0, 11.1, -4.4, -4.5, -4.6, -5.1. IR (Film) υ_{max} = 2956, 2930, 2885, 2857, 1759, 1726, 1699, 1472, 1384, 1361, 1252, 1082, 992, 927, 836, 777, 734. **Rotation:** $[\alpha]^{20}_D$ = -42.7 (c = 1.2, $CHCl_3$)

15-O-Protection Removal



Example: R_2 = TES, R^3 = TBS, R^4 = Troc

68 mg (0.074 mmol) of 19 is dissolved in a polypropylene reaction vessel (with a cover) in 2.5 ml of absolute THF and mixed with 2.5 ml of a standard solution of HF-pyridine (produced from: 5 ml of HF-pyridine, 15 ml of pyridine and 10 ml of THF) that is buffered with pyridine. After 30 minutes, the reaction is completed. For working-up, 80 ml of saturated $NaHCO_3$ solution is introduced, and the reaction mixture is carefully added (plastic syringe) while being stirred vigorously. After extraction with ether (4 times 25 ml) and drying ($MgSO_4$), the solvent is removed in Rotavapor, whereby the pyridine is removed by repeated spinning-in with toluene. The residue is put on a column with deactivated silica gel (hexane/ethyl acetate 2:1 → 1:1), and 51 mg (92%) of product 20 is obtained as a pale yellow, viscous oil.

Compound 20 (R^3 = TBS, R^4 = Troc)

^1H NMR (400 MHz, $CDCl_3$) δ = 9.74 (s, 1H), 6.95 (s, 1H), 6.60 (s, 1H), 4.84 (d, J = 12.0 Hz, 1H), 4.75 (dd, J = 7.8, 4.3 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.41-4.35 (m, 1H), 4.34 (t, J

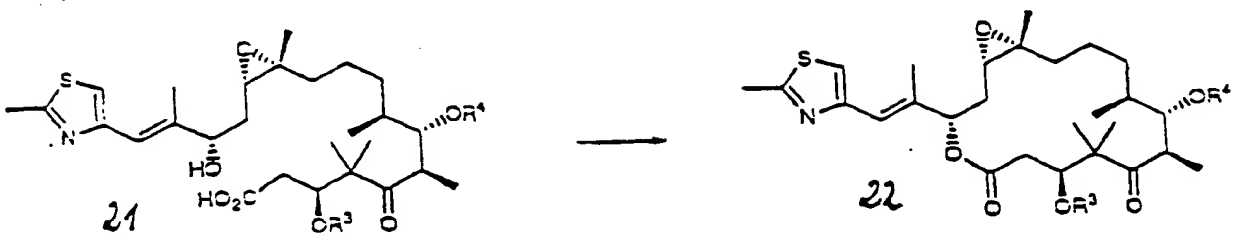
= 4.8 Hz, 1H); 3.49-3.41 (m, 1H), 2.96 (dd, J = 8.0, 4.0 Hz, 1H), 2.96 (s, 3H), 2.67 (dd, J = 17.5 Hz, 4.0 Hz, 1H), 2.40 (ddd, J = 17.5, 5.5, 2.0 Hz, 1H), 2.09 (d, J = 3.5 Hz, 1H), 2.06 (s, 3H), 1.94 (ddd, J = 14.6, 8.5, 4.0 Hz, 1H), 1.78-1.68 (m, 1H), 1.67 (ddd, J = 14.0, 8.0, 4.0 Hz, 1H), 1.58-1.41 (m, 4H), 1.35-1.25 (m, 1H), 1.34 (s, 3H), 1.28 (s, 3H), 1.07 (d, J = 6.5 Hz, 3H), 1.04 (s, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.11 (s, 3H), 0.03 (s, 3H), ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 215.4, 200.5, 164.6, 154.2, 152.7, 141.7, 118.9, 94.7, 82.3, 76.7, 75.4, 72.2, 61.8, 60.7, 53.4, 49.3, 42.2, 34.9, 34.1, 33.2, 32.0, 25.9, 23.0, 22.6, 22.1, 20.0, 19.2, 18.1, 15.9, 14.5, 11.2, -4.4, -4.5.

Pinnick-Oxidation/Macrolactonization

Example: R^3 = TBS, R^4 = Troc

54 mg (0.068 mmol) of aldehyde 20 is dissolved in 2.5 ml of tBuOH and 2.5 ml of 2,3-dimethyl-2-butene and mixed with a solution of 30 mg of $NaClO_2$ and 30 mg of NaH_2PO_4 in 0.5 ml of H_2O and stirred for 45 minutes at room temperature. For working-up, the reaction mixture is mixed with 20 ml of semi-saturated NH_4Cl solution and extracted with methylene chloride (4 x 10 ml).

After drying, the solvent is removed, and crude acid 21 (51 mg) that is thus obtained is used directly in the next reaction.



51 mg (0.062 mmol) of crude acid 21 is dissolved in 1.5 ml of absolute THF and mixed at 0°C with 57 µl (0.36 mmol) of triethylamine and 43 µl (0.24 mmol) of 2,4,6-trichlorobenzoyl chloride and stirred for 20 minutes at room temperature. The active ester that is thus produced is slowly added in drops (15 minutes) to a solution of 80 mg (0.60 mmol) of DMAP in 35 ml of absolute toluene and stirred for 2 hours at room temperature (25°C). The reaction mixture is concentrated by evaporation to about 5 ml and filtered on a short silica gel column (rewashed with 30 ml of hexane/ethyl acetate). Removal of the solvent and subsequent column chromatography (hexane/ethyl acetate 4:1) yield 18 mg (34%) of macrolactone 22 as a colorless oil.

Compound 22 (R^3 = TBS, R^4 = Troc)

^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.99 (s, 1H), 6.56 (s, 1H), 5.21-5.14 (m, 2H), 4.87 (d, J = 12.0 Hz, 1H), 4.75 (d, J = 12 Hz, 1H), 4.05 (d, J = 9.8 Hz, 1H), 3.30 (dq, J = 10.2, 6.3 Hz, 1H), 2.82 (dd, J = 10.3, 4.0 Hz, 1H), 2.79 (dd, J = 16.5, 1.5 Hz, 1H),

2.71 (s, 3H), 2.64 (dd, J = 16.5, 10.0 Hz, 1H), 2.25-2.21 (m, 1H), 2.11 (s, 3H), 1.93-1.64 (m, 4H), 1.55-1.42 (m, 2H), 1.32-1.24 (m, 1H), 1.28 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 1.16-1.08 (m, 1H), 1.12 (d, J = 6.7 Hz, 3H), 1.03 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H), 0.16 (s, 3H), -0.03 (s, 3H).

Protection Removal at 3-O

Example: R^3 = TBS, R^4 = Troc

18 mg (23 µmol) of macrolactone 22 is dissolved in 0.5 ml of THF and mixed with 2.5 ml of buffered HF-Py (see above) and stirred for 72 hours at room temperature, and then it is added carefully to 35 ml of a saturated $NAHCO_3$ solution and extracted with ether. Removal of the solvent (repeated spinning-in with toluene) and subsequent column chromatography (hexane/ethyl acetate 2:1 → 1:1) yield 5 mg (32%) of desired product 23 as a colorless oil. At the same time, 6 mg of starting material is recovered.

Compound 23 (R^4 = Troc)

^1H NMR (250 MHz, $CDCl_3$): δ = 6.99 (s, 1H), 6.63 (s, 1H), 5.52 (t, J = 4.5 Hz, 1H), 5.18 (dd, J = 9.0, 2.0 Hz, 1H), 4.84 (d, J = 12 Hz, 1H), 4.78 (d, J = 12 Hz, 1H), 4.15-4.05 (m, 1H), 3.79-3.70 (m, 2H), 3.64-3.52 (m, 1H), 2.87 (t, J = 6.0 Hz, 1H), 2.72 (s, 3H), 2.59 (dd, J = 14.0, 10.0 Hz, 1H), 2.48 (dd, J = 14.0, 4.0 Hz, 1H), 2.35 (t, J = 7.5 Hz, 2H), 2.12 (s, 3H), 2.00 (t, J = 5.5 Hz, 2H), 1.89-1.81 (m, 2H), 1.75-1.25 (m, 3H), 1.39 (s, 3H), 1.28 (s, 3H), 1.15 (d, J = 7.0 Hz, 3H), 1.09 (s, 3H), 0.99 (d, J = 7.0 Hz, 3H).

7-O-Protection Removal → Epothilone B

Example: R^4 = Troc

2.7 mg (4.4 µmol) of 23 is dissolved in 1.5 ml of ethanol, mixed with 25 mg of NH_4Cl and 25 mg of zinc (powder) and refluxed for 30 minutes. After cooling to room temperature, it is filtered on Celite, washed with ethyl acetate, and the solvent is removed in Rotavapor. Subsequent column chromatography (hexane/ethyl acetate 1:1) yields 1.4 mg (about 90%) of 24 (epothilone B).

Compound **24** (Epothilone B)

^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.97 (s, 1H), 6.60 (s, 1H), 5.41 (d, J = 7.8, 2.4 Hz, 1H), 4.27-4.18 (m, 2H), 3.77 (s, 1H), 3.30 (m, 1H), 2.81 (dd, J = 7.5, 4.5 Hz, 1H), 2.70 (s, 3H), 2.65 (sbr, 1H), 2.54 (dd, J = 14.0, 10.2 Hz, 1H), 2.37 (dd, J = 14.0, 3.0 Hz, 1H), 2.13-2.05 (m, 1H), 2.09 (s, 3H), 1.92 (ddd, J = 15.3, 7.7, 7.7 Hz, 1H), 1.78-1.68 (m, 2H), 1.55-1.46 (m, 2H), 1.45-1.33 (m, 2H), 1.37 (s, 3H), 1.30-1.22 (m, 1H), 1.28 (s, 3H), 1.25 (s, 3H), 1.17 (d, J = 6.7 Hz, 3H), 1.08 (s, 3H), 1.01 (d, J = 7.0 Hz, 3H).

NMR data are identical to the data of K. C. Nicolaou and A. Mantoulidis (Tet. Lett. 39 (1998) 8633-8636). HPLC analysis with a comparison sample of A. Mantoulidis shows identical material.

Preparative Methods:

All reactions of organometallic reagents and all reactions in absolute solvents are performed in an air-free and moisture-free environment. The glass equipment that is used is heated several times in a vacuum (about 0.01 mbar) before the beginning of the test and aerated with dry argon of the Linde Company. Unless otherwise indicated, all reaction batches are stirred magnetically.

Methylene chloride is predried on a basic aluminum oxide column of activity stage I (Woelm) and made absolute on calcium hydride. After predrying on a basic aluminum oxide column over an 8:1 sodium/potassium alloy, diethyl ether is refluxed until stable blue coloring of the benzophenone indicator is achieved, and it is freshly distilled off before use. The tetrahydrofuran (THF) is predried over KOH, filtered on a column that is coated with basic aluminum oxide and then distilled on potassium with triphenylmethane as an indicator.

After predrying over calcium chloride just like hexane (Hex) before use for column chromatography in a rotary evaporator, the ethyl acetate (EE) is distilled off.

Chromatographic Process:

All reactions are monitored by thin-layer chromatography (TLC) on silica gel-60-aluminum foils with UV-indicator F_{254} of the Merck Company. As a mobile solvent, in most cases solvent mixtures that consist of hexane (Hex) and ethyl acetate (EE) are used. For visualization of non-UV-active substances, in most

cases anisaldehyde/glacial acetic acid/sulfuric acid (1:100:1) has been taken as a standard dip reagent.

The preparative column chromatography is performed on silica gel-60 of the Merck Company (0.04-0.063 mm, 230-400 mesh), whereby solvent mixtures that consist of hexane (Hex) and ethyl acetate (EE) or diisopropyl ether are used as eluants.

On an analytical scale as well as on a preparative scale, the high-pressure liquid chromatographic separations (HPLC) are performed on modular systems of the Knauer Company (pump 64, UV and RI detectors, columns and recorders), Waters/Millipore Company (injection system U6K9) and Milton-Roy (integrator CI-10). For the analytical HPLC, in most cases a Knauer column (4·250 mm) with 5 µm of nucleosil is used, and for the preparative HPLC, a column (16·250 mm, 32·250 mm or 64·300 mm) with 7 µm or 5 µm nucelosil 50 is used.

Dye Reagents

Dye Reagent I (F I): In the case of most compounds that can be reduced, 1 g of cerium(IV) sulfate in 10 ml of concentrated sulfuric acid and 90 ml of water yield an intensive blue color reaction during drying.

Dye reagent II (F II): A 10% ethanolic solution of molbydatophosphoric acid represents another dip reagent for detecting unsaturated and reducible compounds. In contrast to dye reagent I, the molybdate dye reagents, especially pertaining to several functionalities, shows a broader color spectrum in the case of virtually identical reliability.

Dye reagent III (F III): 1 ml of anisaldehyde in 100 ml of ethanol and 2 ml of concentrated sulfuric acid represents an extremely sensitive dye reagent that in addition also shows probably the broadest color spectrum.

Dye reagent IV (F IV): Like the anisaldehyde reagent, 1 g of vanillin in 100 ml ethanol and 2 ml of concentrated sulfuric acid is a very sensitive dye reagent with a broad color spectrum.

Dye reagent V (F V): 1 g of 2,4-dinitrophenylhydrazine in 25 ml of ethanol, 8 ml of water and 5 ml of concentrated sulfuric acid represent an excellent dip reagent that responds selectively to aldehydes even without being heated and that responds somewhat more slowly to ketones.

Dye reagent VI (F VI): A 0.5% aqueous solution of potassium permanganate indicates groups that can be oxidized by decolorization, whereby unsaturated, non-aromatic structural units react spontaneously without heating.

Spectroscopic Process and General Analysis:

NMR-Spectroscopy

The ^{1}H-NMR spectra are recorded as an internal standard with a DRX 250 DRX 400 spectrometer of the Bruker Company with the substances as a solution in deuterated solvents and tetramethylsilane. The evaluation of the spectra is carried out according to rules of the first order. If a signal multiplicity that occurs cannot be explained in this way, the indication of the observed line set is done. To determine the stereochemistry, the NOE-spectroscopy (Nuclear Overhauser Effect) is used.

To characterize the signals, the following abbreviations are used: s (singlet), d (doublet), dd (double doublet), ddd (6-line system with two identical coupling constants or an 8-line system in three different coupling constants), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), m (multiplet), mc (centered multiplet), br (broad), hv (semi-masked signal) and v (masked signal).

The ^{13}C NMR spectra are measured as an internal standard with an AC 250 of the Bruker Company with a $CDCl_3$ signal at 77.0 ppm, whereby the proton resonances are wideband-coupled.

IR-Spectroscopy

The infrared spectra are recorded with devices of the Perkin-Elmer Company (model 257 or 580 B) and Nicolet Company (FTIR-interferometer system 55XC). The oils are measured as films between potassium bromide disks. The bands are indicated according to decreasing wave number (cm^{-1}). For characterization, the following designations are selected: vs (very strong), s (strong), m (medium), w (weak).

Abbreviations:

abs.: absolute, **Ar:** aryl/aromatic compound, **Cld.:** calculated, **Brine:** cold, saturated common salt solution, **nBuLi:** nbutyllithium, **c:** concentration, **COSY:** correlated spectroscopy (correlated spectroscopy), **CSA:** camphersulfonic acid, **TLC:** thin-layer chromatography, **DCM:** dichloromethane, **DDQ:** dichloro-dicyano-quinone, **d.e.:** diastereomeric excess, **DIBAH:** diisobutyl-

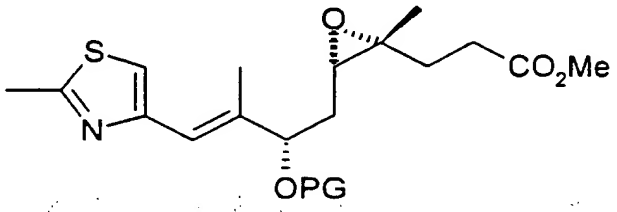
aluminum hydride, **DIPA:** diisopropylamine, **DMAP:** dimethylaminopyridine, **DMF:** N,N'-dimethylformamide, **DMS:** dimethyl sulfide, **DMSO:** dimethyl sulfoxide, **ds:** diastereoselection, **EA:** elementary analysis, **e.e.:** enantiomeric excess, **EE:** ethyl acetate, **EI:** electron impact ionization, **eq:** equivalent(s), **eV:** electron volt, **FG:** functional group, **FI:** field ionization, **gef.:** found, **ges.:** saturated, **h:** hour(s), **Hex:** n-hexane, **HMDS:** hexamethyldisilazide, **HPLC:** high-pressure liquid chromatography, **Hünig Base:** N-ethyl-diisopropylamine, **HRMS:** high resolution mass spectrometry, **HV:** high vacuum, **iPrOH:** 2-propanol, **IR:** infrared spectrometry/infrared spectrum, **J:** coupling constant, **LDA:** lithium diisopropylamine, **Lsg.:** solution, **Lsm.:** solvent, **MC:** methylene chloride, **Me:** methyl, **MeLi:** methyllithium, **min.:** minute(s), **MS:** mass spectrometry/mass spectra, **NMR:** nuclear magnetic resonance, **NOE:** Nuclear Overhauser Effect, **PCC:** pyridinium chlorochromate, **PG:** protective group, **Ph:** phenyl, **ppm:** parts per million, **Rkt.:** reaction, **rt.:** retention time, **RT:** room temperature (20-30°C), **Std.:** hour(s), **TBAF:** tetra-n-butylammonium fluoride, **TBDPS:** tert-butyldiphenyl-silyl chloride, **TBDPSCl:** tert-butyldiphenyl-silyl chloride, **TBS:** tert-butyldimethyl-silyl chloride, **TBSCI:** tert-butyldimethyl-silyl chloride, **TBSTriflate:** tert-butyldimethyl-silyl-triflate, **TEA:** triethylamine, **tert/t:** tertiary, **TFA:** trifluoroethanoic acid, **TFAA:** trifluoroethanoic acid anhydride, **TFMS:** trifluoromethanesulfonic acid, **THF:** tetrahydrofuran, **TMS:** trimethylsilyl-, **u:** $g \cdot mol^{-1}$.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. In a process for the production of epothilone compounds, the improvement comprising preparing said compounds by cyclization of a compound produced from an intermediate of formula II



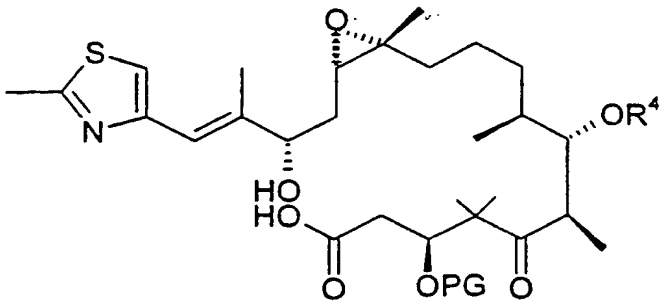
II

wherein PG is a protecting group.

2. The process according to claim 1, wherein PG is a TBS or TES group.

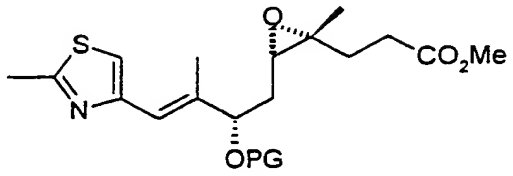
3. The process according to claim 1, wherein the compound of formula II contains a TBS group as PG, which group is changed to a TES group during the process.

4. The process according to claim 1, wherein said cyclization reaction is of a compound of the formula 21



21

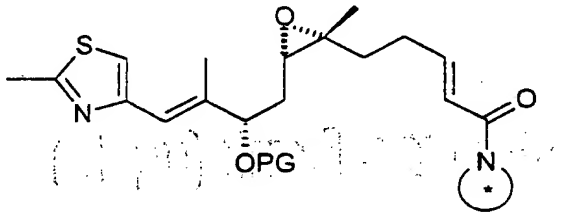
5. The process according to claim 4, wherein the compound of formula 21 is produced by a process comprising reducing a compound of formula 11



11

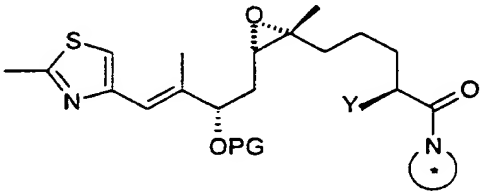
to form an aldehyde, coupling the aldehyde with a compound

to produce an enoylsultam of formula 12,



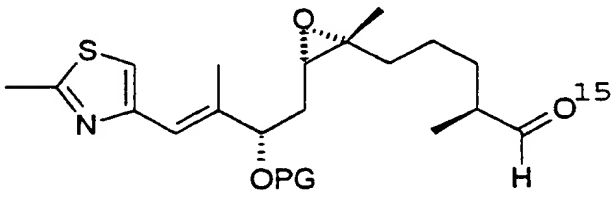
12

reacting enolysultam 12 with L-selectrides to produce compounds of formulae 13 and 14,



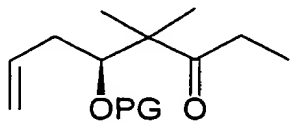
13 (Y=Me)
14 (Y=H)

reducing sultam 13 to form aldehyde 15,



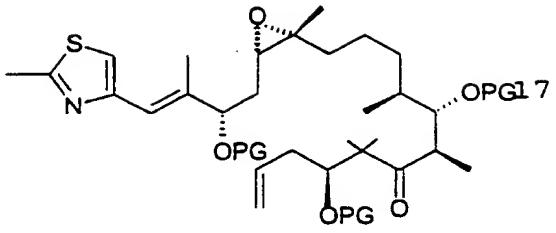
15

reacting 15 with ketone 16

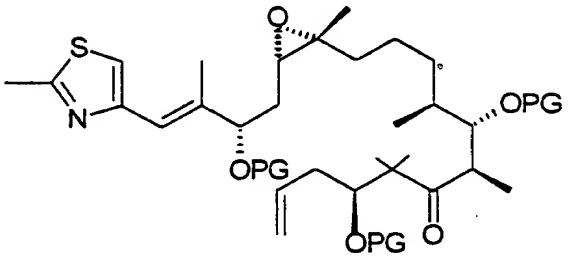


16

to form compound 17,

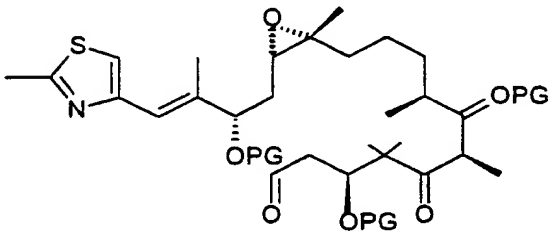


protecting the 17-OH group of compound 17 so as to produce alkene 18,



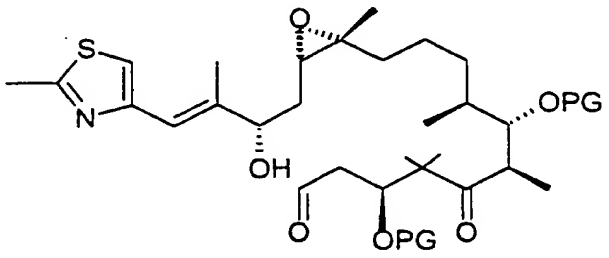
18

subjecting alkene 18 to dehydroxylation and glycocleavage to produce aldehyde 19,



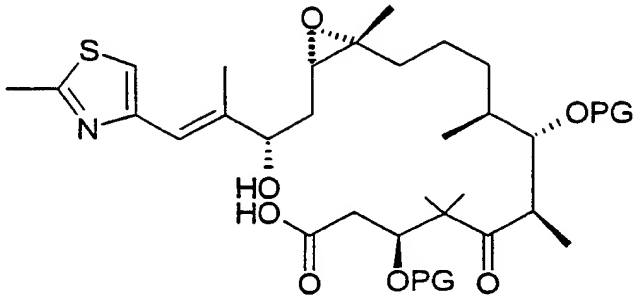
19

deprotecting the 15-position of aldehyde 19 to produce aldehyde 20,



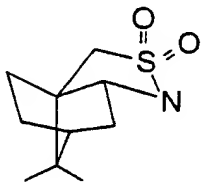
20

and subjecting aldehyde 20 to oxidation and macrolactonization to produce compound 21

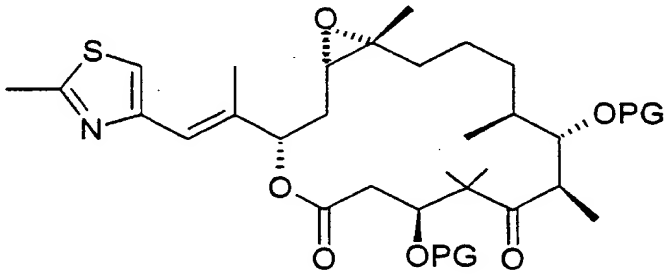


21

wherein each PG independently is a protecting group,

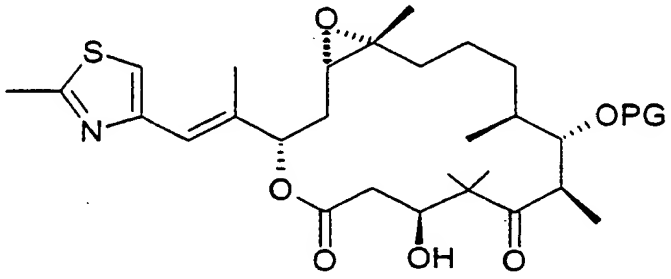
and  is 

6. A process according to claim 4, comprising cyclizing a compound of formula 21 to produce a macrolactone of formula 22



22

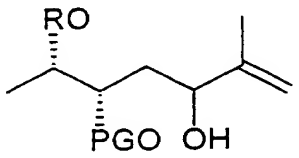
deprotecting the oxygen atom at the 3-position to form a compound of formula 23



23

and removing the protecting group at the 7-position to form epothilone B.

7. A compound of the formula 5 to 21



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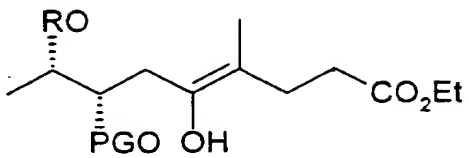

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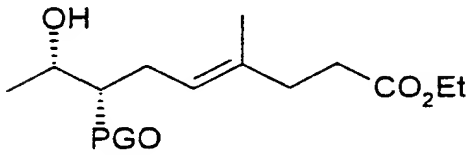

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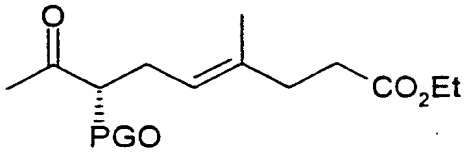

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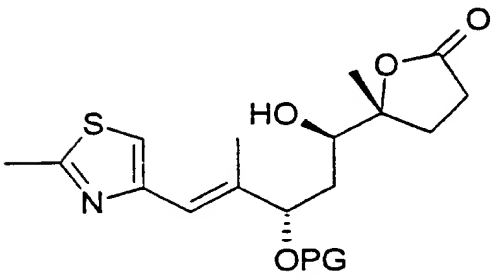

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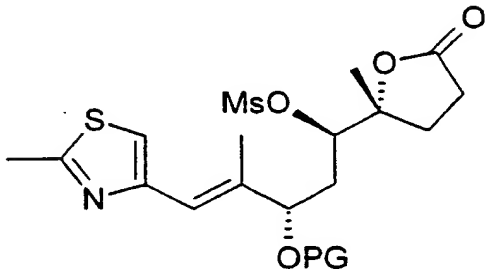

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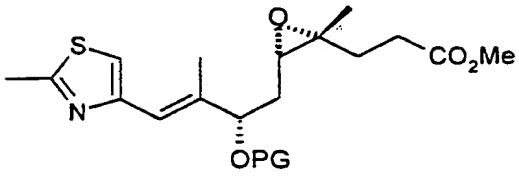

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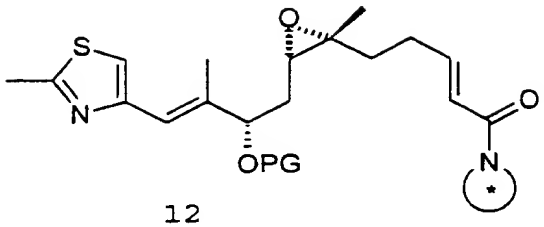

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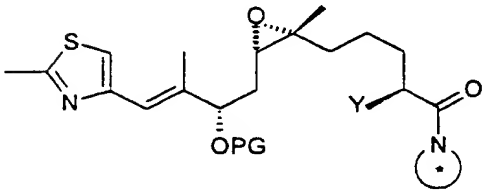
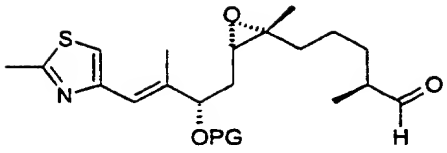


13 (Y=Me)

14 (Y=H)



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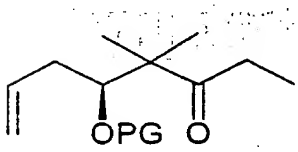

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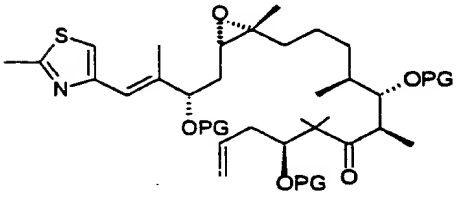

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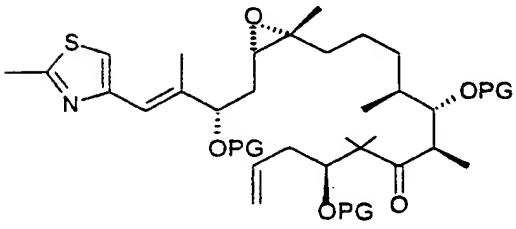

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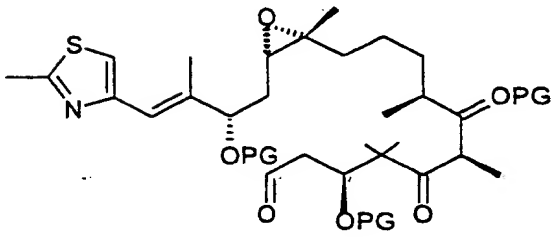

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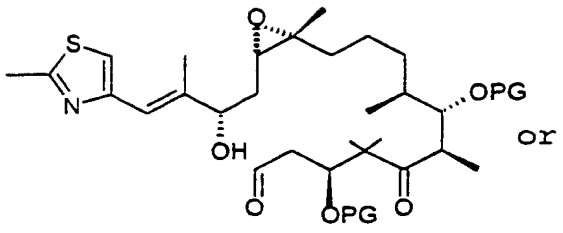
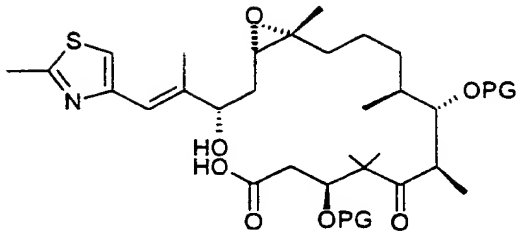


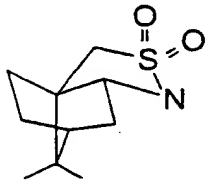
or



20 21

wherein PG is a protecting group,

-N* is



and R is Bn or PMB.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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1 February 2001 (01.02.2001)

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(10) International Publication Number
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(21) International Application Number: PCT/US00/20064

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(25) Filing Language: English

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(30) Priority Data:
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(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
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Filed on 22 July 1999 (22.07.1999)

(71) Applicant *(for all designated States except US)*: **SCHERING AKTIENGESELLSCHAFT** [DE/US]; D-13342 Berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MULZER, Johann** [DE/DE]; Friedridsthaler Weg 20, D-13467 Berlin (DE). **MARTIN, Harry** [DE/AT]; Westbahnstrasse 56/2/8, A-1070 Wien (AT).

(74) Agents: **SHUBIN, Harry, B.** et al.; Millen, White, Zelano & Branigan, P.C., Arlington Courthouse Plaza 1, Suite 1400, 2200 Clarendon Boulevard, Arlington, VA 22201 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

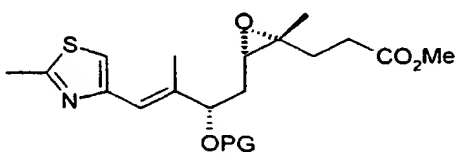
Published:
— *With international search report.*

(88) Date of publication of the international search report:
3 May 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/07439 A3

(54) Title: PROCESS FOR THE PRODUCTION OF EPOTHIOLONE B AND DERIVATIVES AS WELL AS INTERMEDIATE PRODUCTS FOR THIS PROCESS



(II)

(57) Abstract: The present invention is directed to a process for the production of epothilone compounds, the improvement comprising preparing said compounds by cyclization of a compound produced from an intermediate of formula (II) wherein PG is a protecting group.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/20064

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/06 C07D493/04 C07D275/06 C07D417/14 C07F7/18
//(C07D493/04,313:00,303:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NICOLAU K.C. ET AL: "Total syntheses of epothilones A and B via a macro-lactonization-based strategy" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 119, no. 34, 27 August 1997 (1997-08-27), pages 7974-7991, XP002156412 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 cited in the application the whole document	1-6
X	page 7975, scheme 2, compound 19	7
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 January 2001	23/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beslier, L

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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